

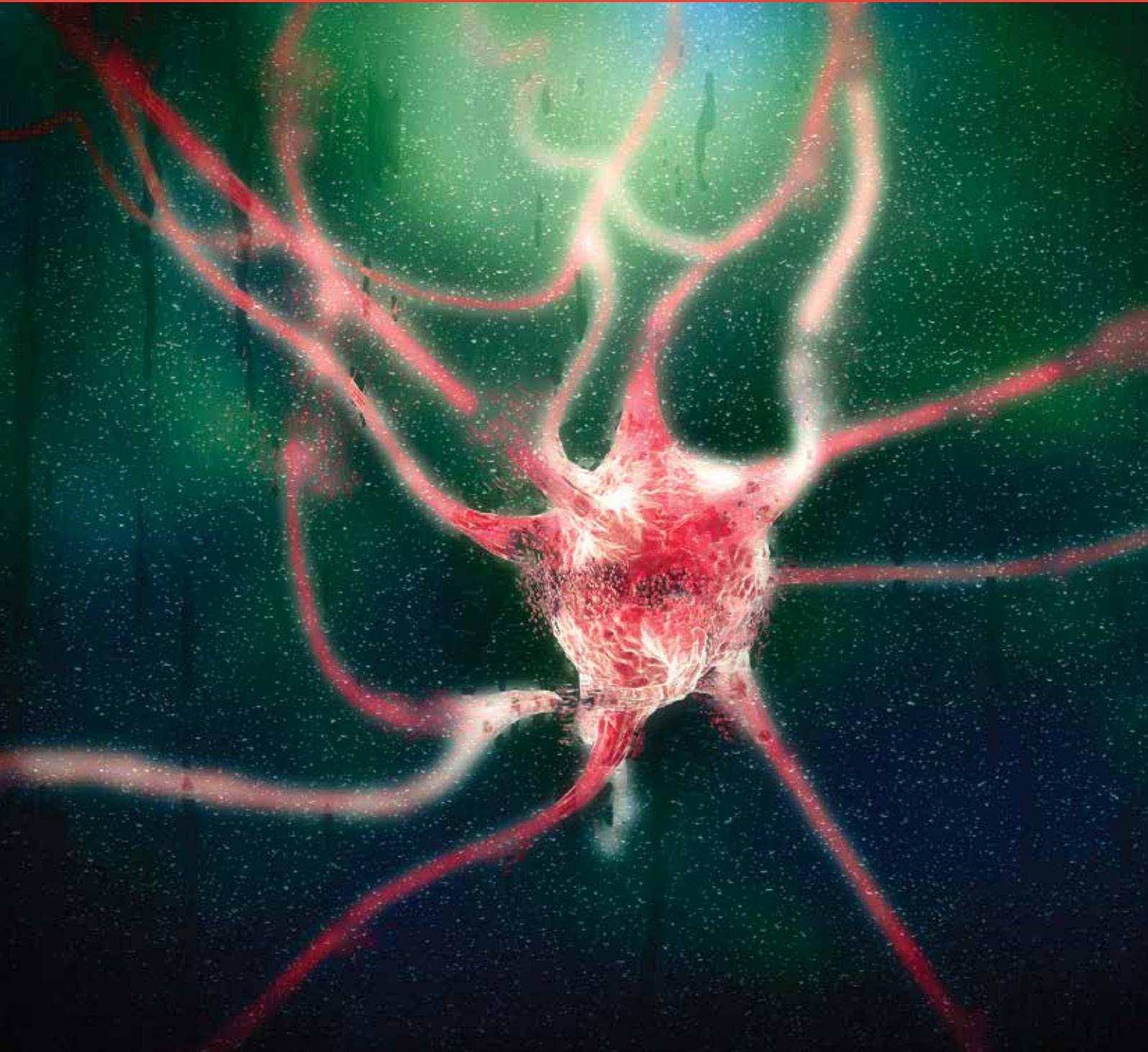


**Alzheimer's Disease  
International**

*The global voice on dementia*

# World Alzheimer Report 2018

The state of the art of dementia research:  
New frontiers



Published by Alzheimer's Disease International (ADI), London.

September 2018

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# Contents

Foreword.....	4
1. Hope & frustration.....	6
2. What causes dementia? The basic science. ....	8
3. The challenges of diagnosis. ....	12
4. When will there be a cure? Drug discovery. ....	16
5. Can I reduce my risk?.....	23
6. Care needed. ....	27
7. Every 3 seconds! The scale of the challenge. ....	32
8. Dementia: It's my story. ....	40
9. Glossary. ....	42

## About the author

Christina Patterson is a writer, broadcaster and consultant. Christina has written for many titles including *Time* magazine and *The Independent* and currently writes for *The Sunday Times* and *The Guardian* in the United Kingdom. She is the author of *The Art of Not Falling Apart*, described by *The Times* as “a beautifully written and uplifting memoir”. The author was supported in the creation of this report by Chris Lynch, Deputy CEO & Director of Policy, Communications & Publications; Annie Bliss, Communications & Policy Officer; Michael Lefevre, General Manager and Wendy Weidner, Research & Policy Project Lead at Alzheimer’s Disease International.



# Foreword



**W**elcome to the 2018 edition of the World Alzheimer Report:

*The state of the art of dementia research: New frontiers.* For many of you, used to reading the World Alzheimer Report each year, this will be a different report in look, in feel and in tone. We have tried to answer a number of complex questions that have been in our minds at Alzheimer's Disease International (ADI). Overall the report aims to clarify whether our call for increased research expenditure in dementia is still relevant and how much so. And indeed it is: compared with the number of people developing dementia – one every 3 seconds – the amounts devoted to research are tiny. For a start there isn't enough original research. The global ratio of publications on neurodegenerative disorders

versus cancer is an astonishing 1:12. At the same time, not enough people are getting into research on dementia. While there are many reasons for this, it is not surprising, given that it has been 40 years since any significant breakthrough. Thirdly, despite a proliferating number of conferences and occasions for exchanging information we have to ask: are researchers and academics really sharing, using and disseminating data and using registries in the best possible way? And is there enough involvement of people in Low and Middle Income Countries (LMICs) in the research process?

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**Are researchers and academics really sharing, using and disseminating data and using registries in the best possible way?**

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Many countries have no diagnostic tools, no access to clinical trials and, indeed, few, if any, specialised doctors and researchers. Where those are present they may not have the means to travel and to communicate their ideas. Yet, with the biggest increases in dementia occurring in LMICs, does this make sense? Shouldn't the governments of those countries try to contribute to research for the benefit of their populations rather than relying on other countries, such as the USA and the UK, to lead the way?

Some of the best and most illustrious minds in Alzheimer's and dementia research have been interviewed by renowned journalist Christina Patterson, who herself has had an important and life-changing family experience of dementia. We hope the resulting report will be an interesting read, both for those in the sector and for those who wonder what is happening in research and why a solution is not being found more quickly. That is not to say that the solution has to be scientific only; dementia is complex and the solution needs to be political and socioeconomic as well.

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## 1% of the societal cost of dementia should be devoted to funding research

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Indeed, research is not just done in labs under microscopes. In the absence of a medical solution, we need more research and innovation around care, especially in domestic settings, as this field will grow both out of necessity and out of a preferred choice of where to live post-diagnosis. We need much more thinking, more research, more innovation and more dynamic entrepreneurship to find solutions.

In short, we hope this will be an interesting and thought-provoking read whether you are in the industry or not, and I thank all participants for taking the time to contribute their great wealth of knowledge to this report. Our hope, as with everything we do, is that it will increase awareness of Alzheimer's disease and dementia and spark a debate which will lead to more governments dedicating funds and focus to help people with dementia and their families live better lives. ADI proposes that, nationally, 1% of the societal cost of dementia should be devoted to funding research in: basic science, care improvements, prevention and risk reduction, drug development and public health. Without significant investments in these areas of dementia research we will be unable to venture into new frontiers.



**Paola Barbarino**  
CEO Alzheimer's Disease International



# 1 Hope & frustration

**Jennifer Bute was shocked when her patients started kissing her.** “Well, you don’t,” she told me with a slightly embarrassed smile, “really hug and kiss the doctor, do you?” A couple of weeks later, she realized that the patient who had hugged her was a friend. “Soon after, I wouldn’t recognise people I had known for 20 years, then I started getting lost along familiar routes. That was kind of how it all started.”

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**Jennifer Bute is one of the 50 million people in the world with dementia, a global community around the size of South Korea or Spain.**

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Jennifer Bute is now 72. She looks younger. Her face is unlined. Her piercing blue eyes still give her the forensic air of a doctor assessing a patient. But she had to give up her work as a GP (a general doctor) when she was 58. At first, it was passwords. She couldn’t remember passwords, or names. One day, she couldn’t find the surgery. Another day, she announced to her guests that dinner was ready and her husband had to tell her that she had already cooked it, and they had eaten it three hours before.

“I diagnosed myself,” she told me. “The first neurologist wouldn’t even do any tests. He said ‘there’s nothing the matter with you.’” But Bute knew there was, and she was right. She now lives in a privately run care village in South West England. “It was still called ‘senile dementia’ when I stopped working,” she said. “Disgraceful! When I was working, very little was actually done proactively about dementia. We didn’t actively search for it. I’m ashamed of how I was as a GP. I didn’t realise what could be done.”

Jennifer Bute is one of the 50 million people in the world with dementia, a global community around the size of South Korea or Spain. About two thirds, like Bute, have Alzheimer’s. Others have vascular dementia, mixed dementia, Lewy body dementia

or frontotemporal degeneration (FTD). All of them have damage to the brain cells that can't be reversed. That community is likely to rise to about 152 million people by 2050, to one that's more the size of Russia or Bangladesh. The current cost of the disease is about a trillion US dollars a year, and that's forecast to double by 2030. This figure includes an estimated cost for "informal" carers, the people who suddenly find themselves acting as 24-hour live in nurses to parents, husbands or wives. The annual global number of informal care is estimated at about 82 billion hours and 71% of these hours are supplied by women.

Alzheimer's disease has taken over from cancer to become America's most feared disease. It kills more people in the US than breast cancer and prostate cancer combined. It's now the number one killer in England and Wales. There's a new case in the world every three seconds. Blink twice, and that's another one. It might be your mum. It might, one day, be you. Oh, and there's no cure.

Since 1998, 100 drugs have been tested and only four have been authorized for use. And these are not magic pills. They can help manage some of the symptoms of dementia, for some people, but only for some people, and most people in the world don't get near them. But anyone who knows anything about the disease knows that there is not going to be a magic pill.

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***“Cure will not,” said Doug Brown, former Chief Policy and Research Officer of the Alzheimer’s Society, “be a silver bullet. A cure for us is either something that can prevent someone from developing dementia in the first place, or can stop dementia in its tracks before it has caused too much damage. It’s likely,” he added, “to be a multiple set of treatments and drugs.”***

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We were sitting in a glass-walled meeting room in the Alzheimer's Society's London office. It seemed to be buzzing. The atmosphere was surprisingly upbeat. Brown joined the organisation six years ago from a research background in malaria, stem cells, HIV and MS. Did he, I asked, notice any differences when he moved into the world of dementia research? Brown nodded and smiled. "What struck me," he said, "even though there weren't any disease-modifying treatments, was the breadth of the research that was happening, and the way that research was happening in such a collaborative fashion, and not just in the UK, but globally."

Over the six months I've spent looking at the world of Alzheimer's and dementia research, and talking to some of its leading lights, I have learnt that he is right. There is a huge amount of research going on globally, in so many different fields. And Jennifer Bute's right, too. There is more that can be done for people with dementia than most people realise. In a field that can look very grim, there are plenty of seeds of hope.



## 2 What causes dementia? The basic science

**S**o, what causes it? What happens in the brain that means that one day you can be the super-efficient executive partner of a large medical practice and the next day you can offer your guests a dinner they have already eaten? That, of course, is the trillion-dollar question, and it's one that doesn't yet have a clear answer.

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**In the past 20 – 30 years, scientists have argued about which protein plays a bigger part in the development of the disease.**

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Most scientists seem to agree that there are two proteins in the brain that are heavily involved. One is beta-amyloid, usually just called amyloid, which reaches abnormal levels in the brain of someone with Alzheimer's and forms plaques that collect between neurons and disrupt cell function. The other is called tau. This also reaches abnormal levels, and forms neurofibrillary tangles inside neurons which block the neuron's transport system. What scientists don't know is exactly how these proteins relate to each other, or what causes them to build to such damaging levels.

"Tau is more like fire in the brain," Alireza Atri told me, "as opposed to amyloid, which is probably a toxic chemical. If you think of a big house or a mansion, and you're spraying this whole toxic chemical around it, it's going to damage things. But really, what causes the huge damage is when you light the match." Atri is an internationally renowned cognitive neurologist and Director of the Banner Sun Health Research Institute and Senior Scientist with the Alzheimer's Prevention Initiative. He is so obsessed with his mission that his car registration number is CUREAD. But he knows, more than most, what a challenge that will be.

So what, I asked, is the kindling? What gets the fire going? There was a pause. “I don’t know,” he said, “if we 100% know that. It’s probably some balance between your own resilience factors and your own vulnerability factors. Some people, somehow, are able to put out that kindling and suppress it. They almost have a better fire extinguishing system in the brain than the rest of us. We don’t,” he said, with a rueful smile, “know why.”

One theory, he explained, is that metabolic factors play a part. The “toxic chemical” of amyloid, he explained, is “probably going to be sort of cooked up by a number of things that are metabolic that all of us will suffer from as we age.” Our ability, for example, to metabolise cholesterol and glucose, plus inflammation, oxidative stress and “the garbage collection system of the brain not working well.” All of those things, he said, probably “help push the amyloid accumulation, which then probably causes damage to the synapses, which causes tau aggregation, which is really the fire”. The main thing we know, in other words, is that the house is on fire, and nobody yet has a clear idea of how to put it out.

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***“We were probably terribly naïve to think a brain disorder like Alzheimer’s disease would be more simple than any other human disorder”***

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In the past 20 – 30 years, scientists have argued about which protein plays a bigger part in the development of the disease. Some have even called themselves “Tauists” or “Baptists”, and have pursued their chosen line with near religious zeal. But that, according to Maria Carrillo, Vice President of the Alzheimer’s Association in the US, has changed. “I think scientists’ minds started opening,” she told me, “when they started realizing that plaques entangled in the brain even before symptoms occur. So both of those are contributors, but what was the real cause? Well, now we understand it’s neurodegenerative, right? That’s the real, ultimate driver of this.”

There are, she said, “many other proteins” involved in Alzheimer’s disease. “The challenge,” she added, “is to understand that it’s very complicated and we may be looking at a heterogeneous activity of ageing that’s associated with this pathological protein that goes awry and calling that Alzheimer’s disease... If you’re really going to make strides in this disease, you’re not going to just be affecting plaques, like we thought before, or tau and tangles. You’re going to have to be looking for a combination approach.”

On the question of complexity, at least, Bart de Strooper, Director of the UK Dementia Research Institute, agrees. He won the 2017 European Grand Prize for Alzheimer Research, and was co-winner, with the neurologist John Hardy, of the 2018 Brain Prize. His work has focused on understanding the fundamental mechanisms that underlie Alzheimer’s and Parkinson’s disease. “We were probably terribly naïve,” he told me when I visited him in his office at University College London, “to think a brain disorder like Alzheimer’s disease would be more simple than any other human disorder, because there is nobody who thinks that diabetes is simple, or that cardiovascular disease is a simple thing.”

De Strooper led a team of 250 researchers at the KE Leuven in Belgium before moving to University College London, and becoming director of the research institute that was started as a result of a pledge coming out of the 2013 G8 summit, championed by the then British Prime Minister David Cameron and former French President Nicolas Sarkozy, to find a “disease-modifying treatment” for Alzheimer’s by 2025. The pledge was made after the 2013 G8 dementia summit, which Cameron chaired. “It’s very nice to promise such things,” said de Strooper, with a distinctly Gallic shrug. “If you’re not in it, you can say what you want. You can even say ‘we’ll get a rocket to the moon in 2025’. If you don’t have to ask how, you can say these things. I like these types of mobilizations, because that will bring the money and the effort. But we are just starting.”

For a Brit, at least, it’s tempting to see de Strooper as the Hercule Poirot of Alzheimer research. You get a sense of his laser focus from his laser gaze. “If you go to PubMed,” he said, “there are three million papers on cancer and there are 250,000 papers on dementia and neurodegeneration. So, we are catching up slowly.”

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***“there are three million papers on cancer and there are 250,000 papers on dementia and neurodegeneration. So, we are catching up slowly.”***

There were, he explained, 10 “golden years”, from about 1990 to 2000, of what’s now called the “amyloid cascade hypothesis”, but the understanding of the basic science was still evolving and “we are starting to see that it’s much more complicated”. If you take away the “biochemical lesions” (the amyloid plaques), that doesn’t take away the effects that have accumulated over 20 odd years. “The challenge to the clinicians,” he said, “is to think about how do we clinically define dementia? Is this really the most productive way to think about these disorders, by looking to the end stage and saying that’s the disease?”

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We need, in other words, to understand brain function at an earlier stage. He thinks the microglia, cells that act as an immune defence in the central nervous system, are an important part of the picture. We need, he said, to see how “different cells talk to each other” and how neurons work together and cause disorder. He thinks the immunology is probably important, as in cancer, and the vascular system, and the gut, and maybe even the bacteria in the gut. It’s an “integrated system”, but progress in science, he explained, is based on tackling one proposition at a time. “Think about Einstein,” he said. “The simpler your theory, the more useful it is to build, and so we need to remain reductionist. We need to dissect this process in small, mechanistic concepts, but we need also to understand that this is a complicated matter.”

It certainly seems to be. Tough, in fact, for a non-scientist like me to grasp. Luckily, there are quite a few world-leading experts who are good at explaining this stuff, and not least to their patients. Christopher Chen, for example, is Director of the Memory Ageing and Cognition Centre at the National University Health System in Singapore. He has done major work in the field of cerebrovascular disease, and in identifying tiny strokes called cortical microinfarcts in living patients, which were previously only seen by neuropathologists, using a microscope. The work he has done, with colleagues in

the Netherlands, has shown that these tiny strokes have an impact on cognition.

He still thinks amyloid is the key. “We are now doing the kind of trials for amyloid we should have done years ago,” he told me. When these trials started, he explained, researchers didn’t have access to the kind of brain scans they have now. They couldn’t, in fact, know that the patients had amyloid in their brain, and later scans sometimes found they didn’t. “If you start a trial where one third of your patients don’t have the target that you’re trying to eliminate,” he said, “you’re really very handicapped. If the anti-amyloid trials in early disease, in patients who have amyloid, don’t succeed, then OK, we’ll get rid of the amyloid hypothesis. But it’s still the best hypothesis we have.”

The consensus, it’s clear, is that amyloid is central to this disease; amyloid and its relationship to tau. What we still don’t know is what causes the amyloid to develop to such abnormal levels. Is it a gene? Certainly, Alzheimer’s can be a genetic disease, with the APOE e4 gene playing a major part in its development. Is it lifestyle? A Lancet report in 2017 claimed that about a third of Alzheimer’s cases are related to lifestyle, to factors like diet, exercise, smoking, alcohol, education and even knocks on the head. What everybody seems to agree is that it’s much more complex than anyone thought. “There’s no one flavour,” Atri told me. “When people say ‘I have cancer’, you always ask them what kind. Even then, you might say ‘breast cancer’. Well, people say: ‘breast cancer, it’s one thing’. But we know it’s not one thing! It’s multiple different things. Dementia is more like that. There are multiple things that go into it.”

There is, it’s becoming all too clear, a long, long path ahead. These people have been working in the field for a long time. They know how big the challenge is. But Ali Atri, as his car registration plate suggests, is deadly serious about meeting it. So is Maria Carrillo. So is Doug Brown, and so were all the people I spoke to for this report.

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***“ We need to believe ourselves,” said Bart de Strooper. “We need to believe that scientific approaches to this problem are going to help. The brain is an organ. It’s a very difficult organ, a very fascinating organ, but it’s made from the same components as all other body parts, and it’s governed by the same principles. So if you can find drugs for cancer, if you can find drugs for heart disease and diabetes, etc., then you should find it for brain disorders, too.”***

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## 3 The challenges of diagnosis

**It was lucky for Jennifer Bute that she was a doctor and could diagnose herself.** Many are not so lucky. There are millions of people around the world who still don't have a diagnosis. We can't be sure of the numbers, of course, because we don't know who they are. It's one of the reasons estimates of what scientists like to call "prevalence", or the proportion of the population who have a certain condition, are - well, estimates. It's also one of the reasons estimates about prevalence in a country like Nigeria vary so much.

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**Forty years ago, Gordon Wilcock started the first multi-disciplinary memory clinic in the UK, while he was a consultant at Oxford.**

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In Lalupon, in the South West of Nigeria, as Adesola Ogunniyi, Professor of Medicine at University College Hospital, Ibadan, explained to me, about 3% of the population are thought to have dementia. In Jos, in the north central region, about 500 miles from Ibadan, the figure is more like 6.4%. Is this massive discrepancy to do with big changes in the risk factors between Lalupon and Jos? Or is it because the main way to diagnose Alzheimer's in a country like Nigeria is to have community health workers knocking on people's doors? And it isn't all that easy to knock on the doors of 180 million people?

Forty years ago, Gordon Wilcock started the first multi-disciplinary memory clinic in the UK, while he was a consultant at Oxford. He also co-founded the UK Alzheimer's Society, which will be celebrating its 40<sup>th</sup> anniversary next year. Even as a child, he told me, he had great respect for older people. His grandfather, who worked on the Great Western Railway, taught him that the most important word in the English language is 'why'. Wilcock, who's now Emeritus Professor of Geratology at the University of Oxford, wanted to bring that questing spirit to geriatric medicine and

change it into a “vibrant, acute” speciality. He is, he said, “fairly pleased” with the progress that has been made. In his 45-year career, he has also seen big changes in the detection and diagnosis of dementia.

“There was no Alzheimer’s disease research when we started out,” he said. “Everybody said it was just what happened to people as part of the ageing process.” For seven years, he led the OPTIMA study, the Oxford Project to Investigate Memory and Ageing, which was one of the first studies to shatter the myth that dementia was a normal part of ageing. In the course of his career, there have, he explained, been two major breakthroughs in the field of diagnosis. “I think standardizing the requirements that are necessary to make a diagnosis has been very important,” he said. “They’ve been around for a long time, but clinicians often didn’t supply them, because they didn’t have the time, or even know about them. Once you actually have a set of agreed standards, even if they weren’t 100% accurate, it meant that people’s minds were more engaged in terms of what they thought was causing the disease.”

## In the course of his career, there have been two major breakthroughs in the field of diagnosis.

He’s talking about the clinical guidelines for dementia diagnosis issued to all doctors in the UK, which are pretty much the same as the ones issued by the NIH, (the National Institutes of Health) in the US. These were updated in 2011 for the first time in 27 years and are currently being reassessed by Alireza Atri and others, as part of a working group for the Alzheimer’s Association. They now include guidelines for the preclinical stage, which are mostly used in a research setting, for MCI, or Mild Cognitive Impairment, and also in some clinics, and for Alzheimer’s and other forms of dementia, where there is clear cognitive decline.

The other major breakthrough, he explained, has been in the field of “biomarkers”, which are measurable indicators of a biological condition. “In my view,” said Wilcock, “the accessibility of structural scanning – CT, PET and MRI – was the major breakthrough, because it took a long time for it to be accepted that it was worth spending the money doing that sort of brain scan on someone with dementia. I think being able to tell that there weren’t other causes of dementia in the brain - vascular disease, say, or a brain tumour - was really quite important.”

CT, PET and MRI scans are computer-generated scans that produce detailed three-dimensional images of the inside of the body – or in this case, the brain. For someone with Alzheimer’s, the main thing you will see is reduced brain mass. On a certain kind of PET scan, you will also see amyloid deposits and inflammatory changes in the brain. The really exciting thing with these scans is that they show that amyloid starts developing in the brain many years before the symptoms set in. Which gives scientists the opportunity to do much better drug research and explore ways of finding how the disease might be slowed, or stopped.

Researchers are also looking at blood and spinal fluid biomarkers and some clinicians are using them, too. “In Scandinavia,” says Wilcock, “they do lumbar punctures

routinely, on pretty well everybody and they measure changes in the spinal fluid, and that's really helpful clinically, too." But a lot of people, he added, are "scared of lumbar punctures". Well, sure. Me too.

For the average person, going to their local doctor, the diagnosis process isn't likely to be straightforward, or quick.

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***" I think the main frustration," he said, "is that if you want to make a diagnosis, you've got to spend a lot of time with the patient, going through their history and examining them, and arranging brain scans and that sort of thing. If a person has had a heart attack, there are tests you can do that show quite conclusively that this person has had a heart attack. We can't do that with Alzheimer's disease yet."***

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At the moment, he explained, the biomarkers are more important in the research context than in the clinic. "In a clinical situation," he said, "if you think someone might have Alzheimer's disease, you can do the scanning as well as take the clinical picture and come up with a fairly robust diagnosis. You might think there's an 80% chance this person has got Alzheimer's, or some other form of dementia, and if you're wrong it isn't a catastrophe, because you're going to do two things. One is to treat the manifestations of their dementia, and that involves the sort of support the NHS and social services give. And you're going to try the Alzheimer's drugs like Aricept or memantine. If they don't work, and you got the diagnosis wrong, it's not a catastrophe."

In a research context, he said, it matters much more. If we're testing drugs on the wrong people, we won't learn what we need to learn. And there are ethical issues, too. "Not everybody who gets amyloid in their brain gets dementia. If you do autopsies on a range of people, particularly older people, there will be amyloid in their

brains, but no clinical evidence that they ever had dementia when they were alive." You might, in other words, be testing heavy-duty drugs, possibly with serious side effects, on people who would never have got the disease in the first place.

It's a minefield. And that's before we even get to home testing, which some people seem to think is next. Does he? Wilcock was polite, but firm. "I don't think," he said, "we're anywhere near it. If you go to a medical clinic with your suspicions, they'll do all these other tests before they come to a decision, and it's most likely to be disease A, B or C. How can someone do that at home?"

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**More diagnosis means more awareness. More awareness means less stigma. Less stigma means more hope.**

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In spite of all the uncertainty, it's clear that things are much better than they were. In Nigeria, for example, huge numbers of people are getting a diagnosis who didn't have one before. Most are not getting PET scans or lumbar punctures, or even much in the way of care. But thousands of healthcare workers are being trained to spot the signs of dementia and they are literally knocking on people's doors. More diagnosis means more awareness. More awareness means less stigma. Less stigma means more hope. And after 45 years of working in the field, Gordon Wilcock is still hopeful. "I am absolutely certain," he said, "that one day we'll sort this out."



## 4 When will there be a cure? Drug discovery

**U**sually, when you get a diagnosis of a disease, you ask your doctor for a pill. But if you've been diagnosed with Alzheimer's, your options will be quite limited. Since 1998, there have been more than 100 attempts to develop an effective drug to treat the disease, but only four have been approved. Yes, four, in twenty years.

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**Since 1998, there have been more than 100 attempts to develop an effective drug to treat the disease, but only four have been approved.**

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There are currently two types of drugs available, which both just aim to treat some of the symptoms. The cholinesterase inhibitors – donepezil, rivastigmine and galantamine, which also have other brand names – all prevent an enzyme called acetylcholinesterase from breaking down acetylcholine, which helps send messages between nerve cells and keep memory going. The other type of drug is called an NMDA receptor. It tries to block the effects of a chemical called glutamate, which is released in excessive amounts in the brains of people with Alzheimer's, and causes damage to brain cells. The generic name for this drug is memantine, but it is also released under other trade names.

The drugs may not be brilliant, but for Jeff Cummings, Director of the Cleveland Clinic at the Lou Ruvo Centre for Brain Health in Las Vegas, the advent of the cholinesterase inhibitors, in 1993 and 1996, was “a paradigm shift” in the field. “The reason I’m so passionate about clinical trials,” he told me, “is that I saw that transition from having nothing to offer to having something to offer and that’s a tremendous difference in terms of the way you interact with families. Now we want ever more powerful drugs.”

Cummings once featured in GQ as a “rock star of science”. From his photo, at least, he looks the part. But if he’s a “rock star”, he’s the kind who has his feet firmly on the ground. In 2014, he wrote a paper in the journal *Alzheimer’s Research Therapy* looking at clinical trials into Alzheimer’s disease drug development from 2002 to 2012. The failure rate, he concluded, was 99.6%. Not exactly cheering, but it hasn’t fazed him. “We know enormously more now than when we started the drug development enterprise,” he told me. “We have scans now, with the amyloid scan and the tau scan, which can define patients much better. We have so much better measurement opportunities in terms of how drugs are working. We’re much more disciplined in our expectations now about what a drug must meet in phase 2 before it can go to phase 3.”

***“We need novel mechanisms of venture capital that could be directed to earlier phases in the pipeline”***

He’s talking about the different stages of drug testing. The first is usually a fairly small trial, looking at how much of the drug it’s safe to give, what the side effects are, how the body copes with it, and what effect, if any, it’s having on its target. The second phase takes things further, and usually involves more people. If this is successful, the drug will move into phase 3, which will involve even more people, is usually randomized and, if successful, will lead to the drug going into development and being licensed for use.

In last year’s report from the Cleveland Clinic, he pointed out that there had only been eight new agents going into phase 1 since 2016. The 2018 pipeline report is, he said, “a little bit better”: twelve this year, but still “way too few”. Funding is the main issue. “Contrast that with cancer,” he said, “where they have hundreds of new agents coming into phase 1. You see that we’re just not generating enough.” The NIH has given a big increase in funding and new agents are being picked up by venture capital. “We need novel mechanisms of venture capital that could be directed to earlier phases in the pipeline,” he explained, “because it’s during those early compounds that it’s most challenging right now.”

In the UK, there’s a good example of what he’s talking about. The Dementia Discovery Fund was set up when David Cameron was chair of the G8 (which later became the G7), as part of the commitment to find a “disease-modifying treatment” by 2025. It’s managed by Kate Bingham and her team at SV Health Managers and has raised £250m from strategic investors, including seven leading pharmaceutical companies, the UK Department of Health, Alzheimer’s Research UK and Bill Gates. Their mandate, Bingham told me, was to do things differently, look at new hypotheses and expand the breadth of targets. “The reason for the 100% failure rate,” she said, “is that the vast majority of therapeutic approaches have been focused around amyloid beta. If we’d invested the same amount of money across 20 different pathways, we may well have seen something like progress.”

Bingham has previously worked with drugs that focus on cancer, autoimmune diseases, infection and inflammation. She has brought neuroscientists from different backgrounds into the team and wants to pursue areas like inflammation, bio-

energetics, the immune system and perhaps even the gut. “Ten years ago,” she said, “we would talk about cancer of the brain or the bowel of the lung or whatever, and now we don’t. We talk about HER2-positive breast cancer or triple negative breast cancer. We talk about the mechanisms that are driving the cancers and we now have drugs that treat these specific mechanisms. So we’ve got a really wonderful roadmap that’s been set out by oncology, to show how really well focused biology can enable much more successful drug discovery.”

By 2025, she hopes to “have multiple drugs showing efficacy”. She also wants to see better use of data analytics, an area that Bill Gates has said he wants to focus on, pulling together different data sets into a central pool. This would help with trials, but also with diagnosis.

This, it turns out, is quite a challenge. Francesca Colombo, Head of Health Division at the OECD, spends quite a lot of her time tackling it. “When we talk about health we’re talking about a sector that’s incredibly data-rich,” she told me. “There are huge amounts of data generated on a daily basis by encounters as well as all the research activities. But this data remains in silos. It’s not shared.” At the OECD, they have done surveys looking at all the different data sets, from hospital data to biobanks, trial registries, data in primary healthcare and in long-term care and support, and found that very few countries were able “to do data linkages across more than three of these data sets on a regular basis”.

There are, she explained, many reasons why it’s so difficult. “There’s the complexity of the data, and technical issues, but also the fact that a lot of it is personal and sensitive data about individuals. I think,” she added, “the main barrier has been trust.” But there are, she said, huge risks in *not* sharing the data. “In talking about

the balance of risk, there’s a tendency to say that there’s a risk of misuse, or breach of privacy or whatever, rather than thinking about the risk for research, but also for surveillance, for better healthcare system management and patient empowerment. Those potential risks from not using data are not really discussed as much.”

The OECD is working hard with governments to help them build better health data governance, looking at data security management systems, legislation and public communication plans. Norway, Finland, the UK, New Zealand, Canada, Israel and Estonia are all, apparently,

making pretty good progress. Others are doing rather less well. “There has been progress,” she said with a sigh, “but not as quickly and not as much as one would hope.”

This is not an abstract issue. Better data would help with trials, but also with diagnosis.

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***“I don’t think Alzheimer’s disease is something like fixing computers or finding a new app”***

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***“ If somebody’s in heart failure,” said Kate Bingham, “you don’t wait for them to have a heart attack to then start treating them. You’ve identified who’s high risk. You’ve put them on statins and an exercise course and told them not to eat too much cake. We don’t do that for dementia. We wait for them to actually have a diagnosis of cognitive impairment before anything happens.”***

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The Dementia Discovery Fund’s approach to drug research is controversial. Bart de Strooper, for example, thinks “they are shooting a lot of shots in the woods, hoping to hit something”. It is, he suggests, too short term. “They are not yet ready to go for 10 years on something,” he told me, “and I don’t think Alzheimer’s disease is something like fixing computers or finding a new app”. But on the broader issues – the parallels with cancer and heart disease, for example – he agrees, and so does pretty much everyone else.

Serge Gauthier, Director of the Alzheimer’s Disease Research Unit at McGill Centre for Studies in Ageing in Canada, has worked in the field for more than 30 years. He has worked on two of the most significant recent international observational studies, ADNI, the Alzheimer’s Disease Neuroimaging Initiative, which he describes as “truly the first collaborative study” and DIAN, the Dominantly Inherited Alzheimer Network, an international research project looking at a rare form of Alzheimer’s that can hit people as early as in their thirties.

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***“ We’re at the point now,” he told me, “where we’re starting to consider that Alzheimer’s disease is a complex of multiple causes and there will not be one drug as a cure. It will be a combination of treatments and we need to have a more subtle and personalized approach.”***

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Like Bingham, he thinks we need to learn from other fields, like rheumatology and cancer. He thinks biomarkers are changing the game. “We’re going to be able,” he told me, and I could hear the excitement in his voice, “like we do now for cancer, to give the right treatment for the right patient, at the right stage of disease. It’s a very different philosophy from 10 years ago.” He is well aware of the need for some of the more cutting-edge scientific research to “translate into therapies that are accessible and affordable”. He wasn’t surprised that tests using one drug haven’t worked on people with late onset dementia. “It was worth trying,” he said, “but we have to change strategy to multi-modal or combination therapy”.

But he is still hopeful that drug treatments on younger people – people with early onset, or even people with no symptoms, but with amyloid in their brains – might show some effect. As Gordon Wilcock pointed out, treating people without symptoms has very big ethical implications. “Sometimes the risks of medications outweigh the risks of getting dementia,” said Gauthier. Tough choices indeed.

Alireza Atri shares Gauthier's scepticism about the likely effects of one drug on patients people with late onset dementia. “By the time we see people, it's organ failure for the brain,” he said. “In which field, when the organ has failed, have we been able to reverse stuff? None. We can't do it for the heart. We can't do it for the liver. The brain is a lot more complicated.” For him, as for Gauthier, the key thing is to detect the disease earlier.

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***“ I think, in the next 5 – 7 years,” he said, “we're going to have absolute breakthroughs in being able to detect the biological disease earlier. Then that's going to give us those opportunities to test drugs much, much earlier. Not just one mechanism, but multiple mechanisms.”***

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To be honest, it's a bit of a rollercoaster talking to the Alzheimer experts. On the one hand, there are all these failed trials and such a complicated picture that it's tempting to go away, pour yourself a giant gin & tonic and have a lie down. On the other hand, they nearly all talk about huge breakthroughs looming, in just a few years. Rachelle

Doody, Global Head of Neurodegeneration at Roche, gets slightly impatient when people talk about failures. She was a professor of neurology running an Alzheimer centre in a medical school for many years before moving to Roche, in Basel, because she wanted to “move the mission along”.

“It does no one any good,” she said, “to talk about 99.6% failures. To me, a failed study is one that you don't learn anything from... Negative studies are very disappointing. They're sad for the participants, they're sad for the patients out there in the public, they're sad for

the investigators and the doctors, but they're *not* failures. They teach us something. Why,” she added, and the passion was rising in her voice, “would a patient be incentivized to be in a trial? If they're told everything's a failure, why would someone invest in the field? If we don't change the rhetoric, we won't get ahead.”

Point taken. Doody is passionate about the role of pharma, too. Pfizer withdrew from Alzheimer research at the beginning of the year, and there are some indications that other drug companies are planning to follow. There have been some very critical voices, including Bart de Strooper, who wrote a piece in *The Guardian* in January about Pfizer's withdrawal from the field. Doody is suspicious of people who criticise

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***“To me, a failed study is one that you don't learn anything from”***

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the industry as a whole. “I don’t see a real distinction,” she said, “between scientists in industry, scientists in academia, scientists in regulatory environments and scientists in public-funding environments. Scientists vary. Some of them are really seeking the truth, and most of them really want to help patients. But some of them are seeking personal glory, and they could be anywhere.”

In her 30-odd year career, Doody has run many trials. She was the principal investigator of donepezil, so she knows a thing or two about running trials well. “The most important thing I learned,” she said, “was to select the trials you offer, so you’re offering something for as many people as possible. Some, for example, on prevention, some focusing on treatment of mild disease, some focusing on treatment of established disease, so people have more than one choice.”

Roche currently has two phase 3 programmes for Alzheimer’s. One is for crenezumab and the other is for gantenerumab, both targeting beta-amyloid with monoclonal antibodies. In phase 2, they have another monoclonal antibody, this time targeting tau. “We made a really tough decision,” said Doody. “If we develop a treatment that works, we want it to be available everywhere. But the way regulatory processes work, we had to start recruiting patients in China before we finished the recruiting for these global studies, or you would never be able to use these drugs there.”

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***“If we develop a treatment that works, we want it to be available everywhere.”***

It’s a reminder of how many things anyone working in this field has to consider. Not just how you find the right drugs, for the right targets, for the right people, at the right time, but how you work within regulatory mechanisms to get those drugs out there. And at a price, we can only (at this stage) hope, that healthcare systems can afford.

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For Maria Carrillo, Chief Science Officer at the Alzheimer’s Association in the US, there’s a key focus that’s often missing. “We forget,” she said, “that a person’s understanding of their own trajectory through a disease should be taken into consideration.” Some patients with late onset disease may not be “the most reliable raconteurs” of their experience, but as researchers move into the area of early onset, or prodromal (pre-symptom) research, we will, she said, “be talking to people that may live many, many years with a full understanding of what’s happening.” She is keen, in other words, that “patient-focused research” means what it says.

The Alzheimer’s Association has made big strides in getting more funding from the US government. “We tell a compelling story,” Carrillo said, “of the great things that happened in cancer, HIV and even heart disease, which resulted in a decrease in the death rate in the United States for those diseases. One of the main reasons we haven’t made progress in Alzheimer’s in many years is because we haven’t funded it.”

When she says, “we haven’t made progress”, she doesn’t mean, of course, that we haven’t made progress at all. As with almost everyone I spoke to, I could hear the excitement about some developments in her voice. “I think,” she said, “the

idea of being able to tackle this disease in its biological stages, its silent stages, is really exciting. And I think our understanding that that means more than just amyloid in terms of trying to find the different targets... is probably the most exciting development we've had in the field."

Just a few weeks after I spoke to her, there was more exciting news. At the end of July, at the Alzheimer's Association International Conference, there were some big announcements. One was that a cholesterol control drug, Gemfibrozil, has been found to reduce amyloid levels and brain inflammation in mice. This is an example of what scientists call "repurposing", testing a drug that's effective in one field, to see if it's effective in another. Another announcement was that a drug called BAN2401 has been found to reduce amyloid in the brain of 81% of patients and slow cognitive decline in the brain of 30%. This is only the second time that a drug that reduces amyloid has also been found to reduce cognitive decline. And the third piece of good news is that crenezumab, the drug Doody told me about, has been found to reduce levels of amyloid in fluid around the brain and the spinal cord. It's early days for all these drugs, but these are certainly signs of hope.

The key message, it's clear, is that everyone just has to keep going.

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***" People ask me," said Jeff Cummings, "when are we going to have a treatment or cure for Alzheimer's disease?". And I tell them: 'I don't know whether it's one step away or 100 steps away, but I do know that you don't get there without taking the next step.'"***

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# 5 Can I reduce my risk?



**N**ow we get to the really, really good news. We may not yet be able to cure dementia, but we can stop people getting it in the first place. Or we might be able to. Not everyone, perhaps, but a fair chunk of the population, and at the very least it looks as though we can delay its onset. Even a five or ten-year delay would have a massive global impact. And this isn't speculation. It's based on solid science.

Miia Kivipelto first became interested in dementia as a child growing up in a small town in Finland. She was sad when her grandmother, who lived with the family, started losing her memory and wanted to do something about it. Kivipelto is now Professor in Clinical Geriatrics at the Karolinska Institute in Stockholm and a senior geriatrician at the Karolinska University Hospital. She was one of the first people in the world to identify the link between lifestyle and dementia. She led the FINGER study, the world's first large multi-dimensional study of lifestyle interventions and now spreads the message that at least a third of Alzheimer's disease is related to factors that can be influenced. The Lancet Report that came out last year put the figure at 35%, but actually Kivipelto thinks the figure could be more like 50%. A world where you could cut Alzheimer's by a half is a world that looks really quite different.

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**A world where you could cut Alzheimer's by a half is a world that looks really quite different.**

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"When I started my PhD in 2002," she told me, "it was quite a fatalistic attitude for Alzheimer's disease. It was mainly high age and genetic factors that were the established risk factors for dementia and Alzheimer's disease, and there was not so much we could do to prevent it. It was fascinating to start thinking 'are there factors you can modify or treat, like we know there are for cardiovascular disease, stroke and diabetes?' So that," she said, "was the starting point."

There had, she explained, been “so many negative trials” for Alzheimer’s disease, both pharmacological and non-pharmacological. “Most of the earlier trials,” she said, “have been so-called single domain trials. Given that there are so many different risk factors and mechanisms behind Alzheimer’s disease, we thought that maybe you need to target several risk factors simultaneously, to get an optimum effect. Something I call multi-domain intervention, so we have the whole package. That’s where we started, in 2009. At that time it was still quite a new area, to work in this way.”

Well, that all, I told her, sounds very impressive, but it’s usually easier to talk about changing a lifestyle than to actually do it. My relationship with my gym, for example, is largely financial. So how did they do it? Kivipelto laughed. “I think our starting point was that you don’t need to change everything at once. We had very good coaches, we had physiotherapists, we had nurses, psychologists, who gave both individual and group sessions. We gave people a lot of support.”

As a half Swede, I know that the Nordic diet is generally pretty healthy anyway, but participants were asked to eat lots of fish, good oils, vegetables, berries and local produce and cut back on milk, cheese, salt and sugar. They tried new recipes. They did some exercise. And the results were spectacular. “After two years, we could see such clear effects,” said Kivipelto, “and that was there for all community domains. We could see it for memory, for their processing speed, how quickly you could do different things. For me, it was a surprise that it was so clear.”

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## They tried new recipes. They did some exercise. And the results were spectacular.

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One of the most exciting results was that people taking part who had the APOE e4 gene, the most important genetic risk factor for Alzheimer’s disease, had even clearer results than those who didn’t. You can’t change your genes, in other words, but that doesn’t mean that you’re doomed.

Kivipelto is now helping to run international versions of FINGER adapted to different cultures, diets and settings.

The one in the US, which will be run with Carrillo and the Alzheimer’s Association, is called POINTER. There’s one in China, one in Singapore and one in Australia. It is, she says, too early to say whether the programme affects beta amyloid levels in the brain, but she is hopeful. She is currently working with the World Health Organization (WHO) on risk reduction guidelines and wants to develop a “tool box”, to translate the research into a practical tool.

“We’ve been talking so much about heart disease and diabetes,” she said, “and people are very worried about the memory problem. Hopefully, that can increase the motivation, that you know that what is good for your heart is good for your brain.”

Well, yes. That message is coming across loud and clear. Most people, in the Western world at least, know that being fat and unfit increases your risk of getting all kinds of diseases, but that doesn’t mean we’re doing what we’re told. Obesity levels are rising. People stare at screens all day, and move less. In Scotland, for example, 65% of adults are overweight, even more than England’s hefty 62%.

Craig Ritchie is Chair of the Psychiatry of Ageing at the University of Edinburgh and Director of the Centre for Dementia Prevention. “You’ve probably heard from Miia,” he said, “that there does seem to have been a reduction in the incidence of dementia in the past five or ten years. This is partly because people of my parents’ generation, in their seventies, did get involved in midlife in things like tests for hypertension and cholesterol levels and they smoke and eat less. But the next wave through is obesity and diabetes. I think that could counteract any of the benefits we’ve seen, in terms of cardiovascular health. Don’t get me started! I’ve lost two and a half stone in the past nine months. Anyone can. It’s motivation!”

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## He cites Scotland’s “golden mile”, where primary school children each have to run a mile a day, as an example of what can be done.

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He cites Scotland’s “golden mile”, where primary school children each have to run a mile a day, as an example of what can be done. He also thinks you have to have things like sugar taxes “because that’s the only way the public health interventions are going to work”. You have, he said, “to do things at a population level, but also at a personal level”. In his own clinic, he is developing personalized prevention plans. “That,” he told me, “relies very heavily on being able to characterize that individual’s risk of getting dementia in the future. For you, it’s the fact that you’re overweight, for you it’s because you’re a boxer and you keep banging your head, for you it’s because you’ve got diabetes. For me, that creates greater salience.”

Ritchie is one of the world’s top authorities on clinical trials in dementia and has been senior investigator on more than 30 drug trials. He’s currently leading the PREVENT project, a UK study aiming to identify mid-life risks for dementia and to look at early changes in the brain. He also leads the EPAD (European Prevention of Alzheimer’s Dementia) Consortium, which aims to build a network of trial delivery centres to carry out ongoing trials on prevention.

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***“ We’re trying,” he told me, “to look at the very, very early stages of the disease. That, of course, is heavily reliant on biomarkers, high grade scanning, spinal fluid, etc. For those individuals who are then deemed to be at high risk, we intervene with drug trials or risk modification, to either prevent the disease from developing any further, or indeed reverse the changes.”***

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That, I told him, sounds like quite a development. “Five years ago,” he said, “no one talked about dementia prevention. Nobody. It’s completely become the thing, and I think that’s a great thing.”

Last year, Ritchie wrote a paper called The Edinburgh Consensus, which came out of a meeting of British experts in neurodegenerative diseases in Edinburgh. The “consensus” was about the importance of identifying the disease in its early stages, since this is likely to be the time when treatments will work best. The paper suggested ways that the National Health Service (NHS) services could adapt to this key development, and be adapted internationally. “It’s a kind of cutting-edge collaboration,” he told me, “of the kind people are always saying we ought to have, but don’t very often... We’re doing it to learn things that can help globally, including in lower- and middle-income countries.”

The key challenge, in terms of trials, he pointed out, was recruitment.

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***“ I’m always struck,” he said, “by the fact that when you do approach people about being involved in research, you almost invariably get a positive reaction.” But it was sometimes hard to get near them to ask them. “I sometimes wonder,” he said, “if regulators think all researchers are evil, and patients have to be protected from us!”***

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It was important, he said, “to create a trial environment where you’re likely to retain people and their willingness and enthusiasm”. He makes sure that there are “participant panels” to help design the trials. Communication is also vital. “There’s a horrible story,” he said, “where a recent trial failed and the first a lot of participants heard about it was on the news. They were still involved in the trial and they heard that the trial had been pulled.”

Ritchie has himself played a major part in redesigning trials. “We were still using methodologies that were so twentieth-century,” he said. “I think that’s where EPAD was really determined to shake it all up and say right, let’s look at these outcome measures again and how we recruit patients and how we define disease early in its course.” He is also doing “adaptive” trials, based on a model used in breast cancer trials where you do regular interim analyses. “You could argue that it’s unethical not to, because you’re going to expose people to a drug where you could have known that it was never going to work. Or you might have a drug that’s working so well, it’s ready to go into phase 3. Why waste two years?”

He has a waiting list in London of 1000 people ready to come into the PREVENT study. “The only thing that stopped us,” he said, “was funding. This whole midlife prevention story narrative has really touched the public.”



## 6 Care needed

**S**o, there are drugs that help, but no cure. There are things you can do to reduce your chances of getting Alzheimer's, and there are exciting developments in drug trials, but what do you do if you've already got it and the drugs, as the Verve once sang, don't work? Or don't work very well?

Many of us assume that if we do get the disease, we will be stuck in front of a TV in a care home. And that, unfortunately, is what does happen to some people, and that's if they're lucky enough to get into a care home in the first place. When this happens, it's nothing less than a tragedy because there is, it's now clear, so much more that can be done.

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**Many of us assume that if we do get the disease, we will be stuck in front of a TV in a care home.**

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Martin Knapp is Professor of Social Policy at the London School of Economics (LSE). He has been researching the economics of non-pharmacological approaches to care for people with dementia, and other conditions related to ageing, for more than 25 years. "I think," he told me, "we're better at recognizing and assessing people's needs and hopefully at least helping them with a label for the distress they're experiencing. And there are some interventions that are being developed in a psychosocial area, around, for example, cognitive stimulation therapy and cognitive remediation and those seem, on average, to work for people in the mild to moderate stage of dementia, in terms of just preserving that cognitive ability for a bit longer."

By cognitive stimulation therapy, he means a programme of themed activities, usually carried out over several weeks in small groups, led by a trained nurse, occupational therapist or carer. In the trials that Knapp undertook, it involved a series of 14

structured 45-minute sessions, twice a week for seven weeks. Each included the same structure, with, say, a warm-up activity, a song, a “reality orientation board”, discussion of current news stories, word games and a practical activity like baking. The trials were found to improve the memory and thinking skills of people with mild to moderate dementia and to improve quality of life. Cognitive remediation is similar, a set of activities which focuses on learning and exercises designed to make your brain work better.

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***“ I think the other thing that’s better,” said Knapp, “is recognizing the roles that family and other unpaid carers play – well, recognizing that they play a role, for a start. And helping those carers with information and advice and sometimes something more therapeutic.”***

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He’s talking about things like START (STrategies for RelaTives), an eight-week programme of individual psychological therapy sessions for carers. The sessions include information on what dementia is, how to manage stress, how to manage difficult behaviour and how to access support. In a randomized control trial, the

programme was found to reduce anxiety and depression for carers in both the short and longer terms. “The research we’ve done,” he said, “suggests that although you have to spend a bit of money upfront to get these interventions established, they pay for themselves quite quickly.”

Knapp agrees that the picture in care homes is often grim, but says that organisations like the Care Quality Commission (CQC), which makes regular inspections, and the National Institute for Health and Care Excellence, which offers evidence-based guidance and advice, have helped push up standards in the UK.

“When my dad had dementia,” he said, “we were looking at care

homes close to where they lived and we could go on the CQC website and look at the quality... And when NICE put out a guideline, the CQC can wave it as a framework when they’re inspecting local services and say ‘why aren’t you doing this?’”

Henry Brodaty, Scientia Professor of Ageing and Mental Health and Director of the Dementia Collaborative Research Centre and Co-Director of the Centre for Healthy Brain Ageing (CHeBA) at the University of New South Wales, wants to make good care homes “business as usual”. In his 40-year career, he has seen plenty. “I wouldn’t want to be in a room with four other people, where everyone’s got the TV on very loud, because their hearing isn’t so good,” he told me. “It’s an awful environment.” But he has also seen homes where people thrive. “They’ve got company, they’ve got stimulation, they don’t have to worry about their own care.” In a care home he visited in Finland, for example, all the residents were making apple pie. “They had sharp knives and were cutting up apples. They had the smell of fresh food in the air.”

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**In a randomized control trial, the programme was found to reduce anxiety and depression for carers.**

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Like Knapp, Brodaty thinks professional caregivers need more training.

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***“ The psychosocial interventions,” he said, “are really doing a lot better than drug taking for people with the behavioural and psychological symptoms of dementia, which people sometimes call BPSD.”***

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So much, he explained, has to do with getting to know the people, their backgrounds, their histories and what they like. He still remembers a man in a care home who used to be a milkman, who would get aggressive every night when the staff tried to put him to bed. “Somebody finally talked to his wife and his wife said: ‘you need to put him in his track suit because that’s what he always did at home. Then he’d wake up at 4am and he’d be ready to hop out of the door and start delivering the milk’. They did it, and it worked like a dream!”

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**When people go into care homes, he explained, they all have care plans, but often the staff don’t look at them.**

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When people go into care homes, he explained, they all have care plans, but often the staff don’t look at them. “We found that the best way,” he said, “is mini tutorials at handover, where you’re talking about the person, and somebody who’s got experience is bringing it to life. In a study we just published, 75% of people were able to be taken off and kept off their antipsychotics for a period of 12 months without any worsening of their behaviours.” The anti-psychotics, he added, “are associated with higher rates of mortality and stroke, and they have other side effects, too.”

Brodaty has seen quite a few different approaches in care homes – things like “doll therapy”, robotic animals, “smile” therapy, aromatherapy, bringing in nursing mothers, bringing in babies, bringing in dogs. Sometimes, they seem to make a difference, but “a lot of these innovative things haven’t had really rigorous research trials to guide them”. He’s more keen on getting the basics right, like proper communication and a focus on the person, not the disease.

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***“ After a dementia diagnosis,” he said, “there should be this whole area of re-ablement. We should be helping people to live positively with dementia.”***

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A big part of that is clearly treating people as the individuals they still are. “Have you ever been on a Club Med holiday?” he asked me. “We used to go with the kids and they had a menu of activities and the kids could choose what activities they could do. Why,” he said, “wouldn’t we have that in nursing homes? Some,” he added, “are already doing it.”

Book me in, I was tempted to say. As a woman without children, I won't be able to rely on extended family, as many in the developing world do. Or perhaps I'll be looked after by a robot? Everyone now seems to think that technology is the answer to everything and the robots, after all, are apparently just waiting to steal our jobs. Kenji Toba, President of the National Centre for Geriatrics and Gerontology in Obu, in Japan, is quite optimistic about the use of robots in care. One of the best, he told me, is a "conversation robot". He showed me a picture, via Skype, and it's tiny. "The caregivers and nurse," he said, "sometimes have to take a long time to hear and speak, but this conversation robot will give 20 minutes of successful conversation. In future, I will teach the robots the personal history of the patient. Maybe the robots can learn hundreds or thousands of personal histories? The nurse," he added, "cannot."

So what, I asked, has it been like for people with dementia when you've tried it? Toba smiled. "Confusing! So far, the friendly nurse or doctor, including me, is better for them." No big surprises there, then. I had, I told him, seen "dementia seals" at a conference at the Science Museum in London. What did he think of them? Toba nodded. "It's good," he said. "Seal robots have an effect on helping a person to become calm. But sometimes in the UK they are using dogs or cats. It's better than using seals!"

Toba also showed me a picture of "Pepper", the robot which is used to teach people with dementia how to dance. There are other robots, he said, that are currently being used to offer music therapy in nursing homes. And he and his colleagues are now studying voice analysis, using AI to identify a patient's mood. "Sometimes," he said, "we use particular examinations, like psychological questionnaires or observations, but if AI can analyse the voice or maybe in future a video analyzing technique to find what's good care and what isn't so good, maybe we can give better care to people with cognitive decline."

Well, maybe, but Toba admits that "robotic trials have big problems". They currently have 23 going on at the research institute, and there have been more than 100 consultations, but so far only five products have gone to market. "It's very difficult for humans," he said. "Their needs are so high. Robotic mechanisms are nice, but sometimes they are not so human-friendly."

This, surely, is at the heart of it all. We need to do things that are "human-friendly". Martin Knapp agrees. "I think," he said, "it's about finding technology-based approaches which are acceptable to the people who are being supported. We did some work a few years ago on telecare for older people, and the challenge was that many older people did not want to have their face-to-face visits with a care worker replaced by some monitoring machine." Where telecare worked best, he said, was for carers, so they could "nip down to the shops" and know that there was a monitoring device to cover for them. The challenge, he said, is going to be when the task being replaced is more personal. "The more important that task is in psychological terms,"

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**There are other robots, he said, that are currently being used to offer music therapy in nursing homes.**

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he said, “the harder it will be.”

For Martin Knapp, as for almost everyone I spoke to, it’s all about treating people as individuals, finding out what they like and what they don’t. Music therapy might help, but it depends what music you like. A project in Birmingham, focused on sporting memories, has been quite successful for older men with dementia. “They’ve got all their Aston Villa stuff from players in the Thirties or Forties or whatever, pictures and so on and they talk about their sporting memories. So, using prompts and positive experiences.” But that, Knapp added wryly, is “assuming your team did well.”

It isn’t complicated, he said. “It’s about what is it that gives me warm vibes in a day, or whatever else. It’s often very small things, or small memories. It’s just trying to find ways of connecting with people in that way.”

His own passion is running. When he’s old, he says, he still wants to be running. When I’m old, I tell him, I still want to be drinking good wine. “It’s your fondness for wine that tells me that care is going to get better,” he said.

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***“ People today have higher and higher aspirations for what their lives will be like. Today’s 60-year-olds are not going to accept the care that today’s 90-year-olds are getting.”***

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# 7 Every 3 seconds! The scale of the challenge



**D**ementia is a human problem and so, of course, it's a global problem. Our estimates about what scientists call "prevalence", or the proportion of people getting it, are getting better, but they are still not nearly good enough. The number of people who have dementia is rising rapidly in low- and middle-income countries, as people live longer. Estimates of prevalence in these countries have been revised upwards as we get better at identifying and diagnosing the people who have it.

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*"In high-income countries the incidence rate, but not necessarily prevalence, may be beginning to come down."*

But it looks as though something different may be happening in high-income countries. "There is some emerging evidence," said Martin Prince, Professor of Epidemiological Psychiatry and Assistant Principal for Global Health at King's College, London, "that in high-income countries the incidence rate, but not necessarily prevalence, may be beginning to come down."

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By "incidence rate", he means the rate at which new cases occur in the population. A smaller proportion of those at risk may develop the condition, but since there are more older people, numbers affected continue to rise. "And that," said Prince, "will be consistent with what we know about the risk factors for dementia and the improvements in cardiovascular health, nutrition and education in high income countries."

We know less, he explained, about trends in low- and middle-income countries, but that's the current focus of the 10/66 Dementia Research Group which Prince helped set up. With 30 research groups in 20 countries in Latin America, the Caribbean, India, Russia, China and South East Asia, the group, which is part of ADI, aims to gather the evidence needed to develop policies to tackle and treat dementia. It was called 10/66 because when it was started only about 10% of the global research on

dementia was taking place in low- and middle-income countries, even though that's where 66% of the people with dementia in the world live. That 66% is set to rise to 71 or 72% by 2050, but the 10% has already shifted to around 50%. "Not in terms of dementia research overall," said Prince, "but most of the interventional research, looking at models of healthcare delivery and social support."

This, clearly, is good news. Also on the positive side, Prince has been among those working with the WHO on the "integrated care for older people" guidelines, which includes people with dementia because "they form the majority of all of those frail older people who need care". On the less positive side, like Craig Ritchie, he is worried that the improvements we've seen in higher income countries in relation to cardiovascular disease and other chronic conditions might start to be offset by big rises in obesity and diabetes. So what, I asked, happens when junk food hits more of the developing world?

## So what happens when junk food hits more of the developing world?

"Exactly," he said. "And smoking rates have been going up over the last 20 years in many of these countries. So there are definitely concerns about public health and what implications that has for health systems that have already been struggling and have to cope increasingly with chronic diseases on top of the diseases of poverty."

With the FINGER study now extending internationally, there are signs, he said, that some of the interventions are having an effect in reducing the incidence of dementia in later life.

***"The theory," he said, "is that if you move it to Mexico or China, where all the evidence shows that problems like hypertension and diabetes are much less likely to be detected and managed appropriately, there's actually much more scope for interventions in those areas, and impact on brain health. So I think," he added, "that's an exciting development."***

Most of the drug research is in the Western world, most of it in North America. "But my take on this," said Prince, "is that let's suppose there's a game-changer, and somebody does actually discover something to change the disease course, all the debates round earlier and timely diagnosis would be completely transformed. Everyone would be wanting a diagnosis, and everyone would be wanting a treatment. That's what happened with HIV. My question is how would that translate into middle-income countries, where currently probably 5 to 10% are actually getting a diagnosis that's timely. So, for me it's around the work that needs to be put into the health system to

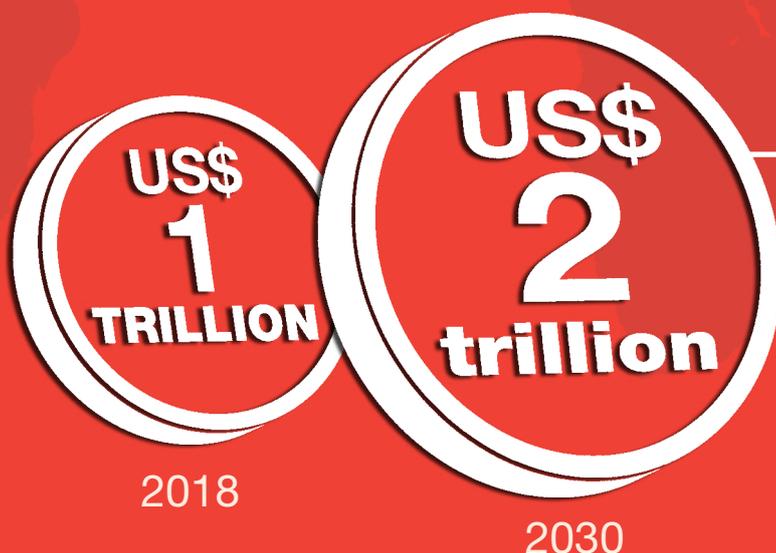
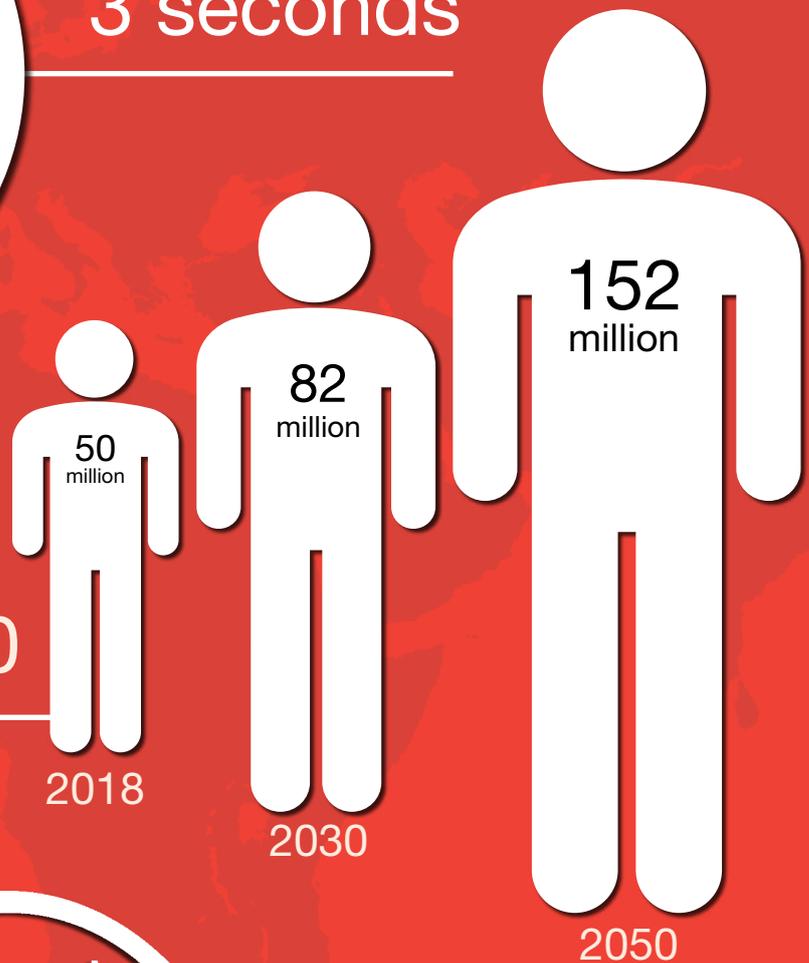
INFOGRAPHIC

# The global impact of dementia



Around the world,  
there will be one new case  
of dementia  
**every  
3 seconds**

50 million people worldwide are  
living with dementia in 2018.  
This number will more than  
**triple to 152  
million by 2050**



The total estimated  
worldwide cost of dementia  
in 2018 is US\$1 trillion.  
This figure will rise to  
**US\$ 2 trillion  
by 2030**

introduce the capacity to provide meaningful assessment and care.”

That’s a question that’s also being asked by STRiDE (Strengthening Responses to Dementia in Developing Countries), a project set up by Martin Knapp and his colleagues, to use economics, epidemiology and policy analyses to help low- and middle-income countries respond to the needs of people with dementia. And it’s a question that people like Adesola Ogunniyi have spent a big chunk of their professional lives both asking and trying to answer.

For the patients at his clinic, Ogunniyi can offer cholinesterase drugs and cognitive stimulation therapy, treat other ailments, like hypertension and diabetes and offer some support to caregivers. But for most people with dementia in Nigeria, this is not an option. Ogunniyi has been developing projects to tackle the issue at community level, projects that could be replicated at mass scale. As part of the IDEA group (Identification and Intervention for Dementia in Elderly Africans), he has developed a protocol for health professionals, community health extension workers and occupational therapists. It’s currently limited to Nigeria and Tanzania, but there are plans to extend it to Zambia, Malawi and Kenya.

He has also developed a form of cognitive stimulation therapy “modified and adapted” to suit the local population. “We introduce them to the old music,” he explained,

***“You have multiple generations, extended family members, all coming together to keep the older person active.”***

“some of the old paper currencies and all those things, just like a reminiscence therapy. They come together and relate as friends and remind themselves of the things they used to do. These have always been very useful and very positive. This is what we are pushing for Africa, rather than spending money on medicines.”

Funding for a number of his projects has been cut. There are other barriers to progress, too. It’s hard to check people’s ages because there aren’t many records. Levels

of HIV infection are still quite high, which can blur study results. It’s difficult for community health workers to reach some villages, because of flooding or rough terrain. And the stigma of having dementia is still high. But Africa does have one big advantage. “We must,” said Ogunniyi, “think of what are the protective factors that may be prevalent in Africa. We think social stimulation... In every household or community, you don’t just have an old person living alone. You have multiple generations, extended family members, all coming together to keep the older person active.”

They are certainly an awful lot cheaper than paying professionals. And the global economy currently depends on the fact that most people who look after people with dementia aren’t paid anything at all. There doesn’t seem to be all that much research on this huge, undervalued resource, or on what can be done to lighten their load, although a recent ADI and Karolinska Institute report estimated that globally, informal care hours equate to 40 million full time equivalent jobs. There is also some interesting research on the use of technology. The INDUCT research study, for example, an

EU-backed collaboration between various European partners including ADI, was set up to look at how technology can be used to help both patients and their carers and is currently investigating the use of voice-activated devices, motion sensors, GPS trackers and intelligent fridges. The Dementia Services Development Centre in Scotland and the Dementia Centre in Sydney are also doing interesting work in this field. But this is small fry for a vast unpaid workforce that's largely unacknowledged, often unvalued and often untrained.

The challenges – and opportunities – Ogunniyi has identified apply to quite a few low- and middle-income countries. In Latin America, for example, there are high levels of deprivation and income inequality, but there are also family structures that mean that people with dementia can get more in the way of social support. “Latin America,” said Ricardo Allegri, Chief of Cognitive Neurology at FLENI in Buenos Aires, “is a very interesting part of the world. There's a big diversity in the population – ethnic diversity, educational diversity, cultural diversity.”

“We have,” he told me, “performed some epidemiological studies in several slums in our country and found that people between 50 and 70 have a higher prevalence

of dementia than in developed countries.” The studies, he explained, took place in a slum district near Buenos Aires and one near San Paolo, and they appear to confirm the view that low levels of education, and healthcare, are likely to lead to higher levels of dementia, and at an earlier stage. While this is clearly bad news for the people who live there, it does offer opportunities to do things that will make a real difference. “We are organizing to collaborate with FINGER,” he said, “with Miia Kivipelto and Maria Carrillo, in a study similar to the ones they have done, to prevent the risk factors in middle age. In low-income

countries,” he added, “I believe prevention is the most important thing you can do.”

Allegri has also worked with the ADNI and DIAN observational studies, in the first collaboration with US research institutes of its kind. It is, he explained, the only major study on dementia in Latin America to focus on biomarkers, but there are plenty of other interesting trials. Francisco Lopera's studies on an extended family in Colombia with early onset Alzheimer's have attracted international attention. And Ricardo Nitrini's studies on dementia in Brazil have played a major part in mapping the condition in a country with a population of more than 200 million. So far, only Chile, Costa Rica and Cuba are implementing national dementia plans, but their populations – around 18 million in Chile, five million in Costa Rica, and 11 million in Cuba – do make the challenge a bit less daunting.

“In our cities,” said Allegri, “you have a big population in a small place.” The same, of course, applies in places like Singapore. Like Allegri, Christopher Chen thinks the focus should be on prevention. “If you would ask me,” he said, “what's going to be the most important thing we can do for the prevention of dementia in Asia, what would you say?” Better diet, I said, and more exercise. Oh, and perhaps education.

**...low levels of education, and healthcare, are likely to lead to higher levels of dementia, and at an earlier stage.**

Chen agreed.

China is making huge advances on that front. It is also doing trials on a scale that nobody else can come near.

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***“China is just amazing,” said Chen. “They have the capacity and the will to show that certain interventions will work... They have been able to do trials on stroke care to show that improving processes, getting people to follow guidelines and protocols, actually makes a difference. So I hope China will show us how we organize ourselves.”***

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Singapore, too, is making huge advances. “We are fortunate,” he said, “in that we are growing richer at the same time as we are growing older.” Patients at his clinic, and many other memory clinics, are assessed by teams of clinicians and psychologists and referred to occupational therapists and physiotherapists for treatment programmes as well as drugs.

But the really impressive thing is what’s happening at governmental level. “They are trying,” said Chen, “to increase the birth rate, and at the same time to make

Singapore a much more friendly place for the elderly.

For example, a lot of thought is being put into reforming or improving the pension system. A lot of thought has been put into improving public housing. There’s a push to design housing for the elderly, in order to allow families to downsize and to live closer to public amenities, so they’re not isolated. And, of course, there’s a lot of investment in healthcare, to improve our ability to cope with the needs of the elderly.”

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***“There’s a push to design housing for the elderly, in order to allow families to downsize and to live closer to public amenities”***

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There are campaigns in public places in Singapore to encourage people to look out for people with dementia,

and be aware of their needs. “We now have campaigns,” said Chen, “in hawker centres and markets, saying that if you see somebody who’s elderly and lost, give them a hand.”

He is talking, of course, about creating a “dementia-friendly” society. Singapore is doing well on this, but the world leaders are Japan. And they have reason to take this seriously. There are five million people with dementia in Japan. It’s the country with the highest life expectancy (currently 84) and the highest proportion of old people in the world. The “dementia-friendly” movement has started in individual cities. In Obu, where Kenji Toba has his clinic, for example, more than 70 companies have started to

look at what they can do. "Within a couple of years," said Toba, "I hope we will spread to the whole of Japan."

Like Singapore, Japan is making huge strides in terms of planning for housing needs, sheltered accommodation and resident-friendly care homes. It has a long-term care insurance scheme which can be accessed by anyone over the age of 65. "Japan," said Toba, "is a dementia society. We have to prepare as soon as possible."

Well, yes. We all do. There is masses going on around the world, but we need to do more. There are plenty of international collaborations, but there's a clear need for more. "International co-operation," said Christopher Chen, "works to give us different ideas, new ideas, that we can try. It helps to validate what we're doing, because it's much more difficult following your own lonely path. It's also very important not just for the morale of the patients and care-givers and the healthcare providers, but also politically. It stiffens our resolve to do something about this."

For Glenn Rees, Chair of ADI and former CEO of Dementia Australia, the most important thing is getting the system right. "I think you can develop models and approaches till the cows come home," he said, "and that's all very valuable, but what really interests me much more is system.

How do things actually fit together? How do you match unique needs to services? What are the strategies, economic and social, that empower consumers to actually get what they need, as opposed to what they might be offered?

He thinks that government-led research should focus on "issues of basic science" and that care research should be led by "consumers" of that care. Not, in other words, people sitting in government or university offices, but the people who actually need it.

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***" I'm old enough," he said, "to remember how cancer was regarded in the 1950s. I've seen the progression in research since then. I've seen the political priority. I've seen the cleverness of the advocacy around cancer. I don't think politicians yet understand the timescale and the immensity of the task."***

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It doesn't look as though they do. Or perhaps they are just taken up with other issues. More than 30 countries, thanks to the work of ADI and other organisations, have adopted national dementia plans, and it's clearly a big step forward that the WHO last year declared dementia a "public health priority". But Glenn Rees is right that we

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## Japan is making huge strides in terms of planning for housing needs, sheltered accommodation and resident-friendly care homes.

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need much better systems. Kenji Toba is right that we need to build dementia-friendly societies. Martin Knapp is right that baby boomers will be more demanding. Miia Kivipelto is right that we need to do more to help people change their lifestyles. Serge Gauthier is right that we will need to be looking at more personalized approaches to medical treatments. Henry Brodaty is right that we will need to be looking at more personalized approaches to care. Maria Carrillo is right that we need to have more trials that reflect the full range of the population. And almost everyone I spoke to was right that we need more, and better, collaboration. But the big issue, the really big issue, is money. We won't be able to do this with current levels of funding.

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***“ If you continue at this level,” Bart de Strooper told me, “there will be nothing in 20 years. We need to become really very, very serious. The Dementia Research Institute is sold to me and the public as a big investment. It’s peanuts! It’s 250 million, but over seven years. Any football team in the premier league has a bigger yearly budget... Scientific talent is no different from football talent. There are people who can score goals, and there are people who can run. If you want to have a real world-leading centre, you need to be able to attract the best.”***

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## 8 Dementia: It's my story

**It's now nearly 10 years since Jennifer Bute diagnosed herself with Alzheimer's.** She has adapted incredibly well. She runs groups for people with dementia, using the brain games developed by the Japanese neuroscientist Ryutu Kawashima. "I call them my Japanese family groups," she told me. "There were some people in the groups who couldn't write their name any more. So we started to teach them to do their letters again, because you can learn." She has a website, full of tips on how to cope, with a video that has been watched 27,000 times. She has written a book, *Dementia from the Inside: A Doctor's Personal Journey of Hope*, which will be published later this year.

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***"When I was diagnosed," she told me, "I thought it was the end of the world, but it's not the end of the world."***

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If she can't do something in the way she used to, she finds another way to do it. "I have a computer," she told me, "which tells me when to do everything, even when to change my bed clothes and things like that. So my routine is always to look at my computer, which tells me what I should be doing that day." Bute can't cope with the phone any more, but she can send emails, and communicate on Facebook or via Skype. She takes part in Zoom cafes, virtual networks for people with dementia around the world. She is busy. She is sociable. She is cheerful.

"When I was diagnosed," she told me, "I thought it was the end of the world, but it's not the end of the world. If you've had a severe stroke, well, you can choose for it to be the end of the world, or you can get up and do something about it."

I wish I could bottle her spirit. I wish we could all share it. But I did sense something like it in all the interviews I did. It was the belief that this was a challenge we can fight. It's a challenge we need to fight now.

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***“ A third of babies born now in Japan,” Kenji Toba told me, “will live to 100 years. The risk of dementia in a centenarian in Japan is 99%. Everyone has to understand ‘it’s my story’. Not your story. ‘Cognitive decline is **my** story.’”***

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And then he got up from his desk and came back with a photo of his grandchildren. They were smiling. They were beautiful. It’s their story, too.

## World Alzheimer Report 2018 Glossary of terms

**“Adaptive” trials** – a clinical trial that observes participant outcomes (and possibly other measures, such as side-effects) on a prescribed schedule, and modifies parameters of the trial protocol in accord with those observations.

**“Integrated care for older people” guidelines** – the World Health Organization’s evidence-based recommendations for health care professionals to prevent, slow or reverse declines in the physical and mental capacities of older people.

**10/66 Dementia Research Group** – a collective of researchers carrying out population-based research into dementia, non-communicable diseases and ageing in low- and middle-income countries.

**ADNI (Alzheimer’s Disease Neuroimaging Initiative)** – a multisite study which began in 2004 that aims to improve clinical trials for the prevention and treatment of Alzheimer’s disease.

**AI (artificial intelligence)** – the ability of computers to simulate intelligent human behaviour.

**Alzheimer’s disease** – Alzheimer’s disease is the most well-known form of dementia and accounts for 50-60% of all cases. It destroys brain cells and nerves disrupting the transmitters which carry messages in the brain, particularly those responsible for storing memories.

**Alzheimer’s Research UK** – a UK-based Alzheimer’s research charity aiming to defeat dementia.

**Amyloid** – a starch-like protein which is deposited in the liver, kidneys, spleen, or other tissues in certain diseases. Often used to describe beta-amyloid (see below).

**Amyloid cascade hypothesis** – proposes that excessive accumulation of amyloid-beta is the key event in Alzheimer’s disease. This is a widely-accepted explanation of the causes of Alzheimer’s disease.

**APOE e4 gene** – this allele is present in approximately 10-15% of people and increases the risk for Alzheimer’s and lowers the age of onset. Having this gene is a risk factor for dementia but does not mean that Alzheimer’s Disease is certain.

**Beta-amyloid** – an amyloid that is derived from a larger precursor protein and is the primary component of plaques characteristic of Alzheimer’s disease.

**Bill and Melinda Gates Foundation (BMGF)** – a private foundation founded by Bill and Melinda Gates, primarily focusing on enhancing healthcare and reducing extreme poverty globally, as well as expanding educational opportunities and access to information technology in the USA.

**Biomarkers** – a naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, etc. can be identified.

**Cancer** – a disease caused by an uncontrolled division of abnormal cells in a part of the body.

**Cardiovascular disease** – a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease, deep vein thrombosis and pulmonary embolism. Cardiovascular diseases are usually associated with a build-up of fatty deposits inside the arteries – known as atherosclerosis – and an increased risk of blood clots.

**Care Quality Commission (CQC)** – the executive non-departmental public body of the Department of Health and Social Care responsible for regulating all health and social care services in England.

**Cerebrovascular disease** – disease of the blood vessels including the arteries that supply the brain.

**Cholesterol** – a compound of the sterol type found in most body tissues. Cholesterol and its derivatives are important constituents of cell membranes and precursors of other steroid compounds, but a high proportion in the blood of low-density lipoprotein (which transports cholesterol to the tissues) is associated with an increased risk of coronary heart disease.

**Cognitive remediation** – a treatment designed to improve neurocognitive abilities such as attention, working memory, cognitive flexibility and planning, and executive functioning.

**Cognitive stimulation therapy** – a treatment which aims to improve cognitive skills and quality of life of people with dementia through activities such as categorisation, word association and discussion of current affairs.

**CT (computerised tomography) scan** – a type of scan that uses X-rays and a computer to create detailed images of the inside of the body.

**Dementia** – Dementia is a collective name for progressive brain syndromes which affect memory, thinking, behaviour and emotion. There are over 200 subtypes of dementia.

**Dementia Discovery Fund** – a specialist venture capital fund that invests in novel science to create meaningful new medicines for dementia whilst delivering an attractive return for the fund investors.

**Diabetes** – a disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood.

**DIAN (Dominantly Inherited Alzheimer Network)** – enables researchers around the world to monitor and identify changes in individuals who carry one of the gene mutations (Presenilin1, Presenilin2 or APP) known to cause dominantly inherited Alzheimer's disease (DIAD).

**Early/younger onset dementia** – any dementia beginning before the age of 65. About 1 person in every 1000 below the age of 65 develops dementia.

**FINGER study** – the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability investigated the effects of a 2-year intervention monitoring 1,260 participants aged 60-77 and targeting several lifestyle and vascular risk factors simultaneously. The main aim is to prevent cognitive impairment.

**Frontotemporal degeneration (FTD)** – Fronto-temporal dementias are a relatively rare cause of dementia and typically develop at an earlier age than Alzheimer's disease, usually in a person in their forties or fifties. The frontal lobe of the brain is particularly affected in early stages and can affect behaviour and personality.

**G7 (formerly G8)** – a group consisting of Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States, which together represent over 62% of global net wealth.

**HER2-positive breast cancer** – a breast cancer that tests positive for a protein called human epidermal growth factor receptor 2 (HER2), which promotes the growth of cancer cells. In about 1 of every 5 breast cancers, the cancer cells have a gene mutation that makes an excess of the HER2 protein.

**High-income countries** – a country with over US\$12,235 Gross National Income per Capita, according to the World Bank 2017-2018 classification.

**HIV** – The Human Immunodeficiency Virus (HIV) targets the immune system and weakens people's defence systems against infections and some types of cancer. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient.

**Hypertension** – a condition in which the blood vessels have persistently raised pressure. Also known as high or raised blood pressure.

**IDEA group (Identification and Intervention for Dementia in Elderly Africans)** – a brief cognitive assessment for dementia and major cognitive impairment in low literacy settings.

**Immunology** – the branch of medicine and biology concerned with the immune system, including its structure and function, disorders of the immune system, blood banking, immunization, and organ transplantation.

**Incidence** – the rate or probability of occurrence – for example a disease – within a population. In other words, the number of new cases of a disease occurring within a population.

**Lewy body dementia** – Lewy body dementia or dementia with Lewy bodies is similar to Alzheimer's disease in that it is caused by the degeneration and death of nerve cells in the brain. It takes its name from the abnormal collections of protein, known as Lewy bodies, which occur in the nerve cells of the brain. Half or more of people with Lewy body disease also develop signs and symptoms of Parkinson's disease.

**Low-income country** – a country with less than US\$1,005 Gross National Income per Capita, according to the World Bank 2017-2018 classification.

**Lumbar puncture** – the procedure of taking fluid from the spine in the lower back through a hollow needle, usually done for diagnostic purposes.

**Malaria** – a life-threatening disease caused by parasites that are transmitted to people through the bites of infected female Anopheles mosquitoes, called “malaria vectors.”

**Middle-income country** – a country with between US\$1,006 to \$12,235 Gross National Income per Capita, according to the World Bank 2017-2018 classification.

**Mild Cognitive Impairment (MCI)** – the stage between the expected cognitive decline of normal aging and the more serious decline of dementia.

**Mixed dementia** – Mixed dementia refers to the condition where abnormalities characteristic of more than one type of dementia occur simultaneously. For example, individuals can have both Alzheimer's disease and vascular dementia together.

**Monoclonal antibodies** – an antibody produced by a single clone of cells or cell line and consisting of identical antibody molecules.

**MRI (Magnetic resonance imaging) scan** – a type of scan that uses strong magnetic fields and radio waves to produce detailed images of the inside of the body.

**MS** – Multiple sclerosis (MS) is a condition that affects your brain and spinal cord. In MS, the coating that protects your nerves (myelin) is damaged, and this causes a range of symptoms linked to the central nervous system.

**National Institutes of Health (NIH)** – the USA's medical research agency, which is part of the US Department of Health and Human Services.

**Neurodegeneration** – degeneration of the neurons in the brain. Many neurodegenerative diseases – including Alzheimer's disease, Parkinson's disease and Huntington's disease – occur as a result of neurodegenerative processes.

**Neurology** – the branch of medicine or biology that deals with the anatomy, functions, and organic disorders of nerves and the nervous system.

**Neuropathologists** – A pathologist who specializes in the diagnosis of diseases of the brain and nervous system by microscopic examination of the tissue and other means.

**NHS (National Health Service)** – the publicly funded national healthcare system for the United Kingdom.

**NMDA receptor (N-methyl-D-aspartate receptor)** – a glutamate receptor and ion channel protein found in nerve cells that is important for controlling synaptic plasticity and memory function.

**Occupational therapist** – a professional who provides practical support to empower people to facilitate recovery and overcome barriers preventing them from doing the activities that matter to them.

**Oncology** – the study and treatment of tumours, normally in the context of diagnosis and treatment of cancer.

**Oxford Project to Investigate Memory and Ageing (OPTIMA)** – a group founded in 1988 with the aim of understanding the causes, treatment and prevention of dementia, especially Alzheimer's disease.

**Oxidative stress** – an imbalance between free radicals and antioxidants in your body.

**PET (Positron emission tomography) scan** – a type of scan that is used to produce detailed 3-dimensional images of the inside of the body.

**Physiotherapist** – a person qualified to treat disease, injury, or deformity by physical methods such as massage, heat treatment, and exercise.

**POINTER (US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk)** – a two-year clinical trial to evaluate whether lifestyle interventions that simultaneously target many risk factors protect cognitive function in older adults who are at increased risk for cognitive decline.

**Prevalence** – the proportion of an occurrence of something – for example a disease – within a total population.

**PREVENT Project** – a prospective cohort study identifying mid-life (aged 40–59) biomarkers of late-onset Alzheimer’s disease.

**Prodromal** – an early sign or symptom(s), which may indicate the onset of a disease.

**Psychosocial** – the combined influence that psychological factors and the surrounding social environment have on individual’s physical and mental wellness and their ability to function.

**PubMed** – a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics.

**Rheumatology** – the study of rheumatism, arthritis, and other disorders of the joints, muscles, and ligaments.

**Risk factors** – factors or characteristics linked to the development of a condition, often linked to lifestyle.

**Spinal fluid** – a fluid that is continuously produced and absorbed and that flows in the ventricles within the brain and around the surface of the brain and spinal cord. The primary function of spinal fluid is to cushion the brain within the skull and to serve as a shock absorber for the central nervous system. It also circulates nutrients and chemicals filtered from the blood and removes waste products from the brain.

**START (STrategies for RelaTives)** – an eight-session manualised intervention aimed at promoting the development of coping strategies for family carers of people with dementia, which aims to reduce depression and anxiety.

**Stem cells** - biological cells that can differentiate into other types of cells and can divide to produce more of the same type of stem cells. Since stem cells have the ability to turn into various other types of cells, scientists believe that they can be useful for treating and understanding diseases.

**Stroke** – a serious life-threatening medical condition that occurs when the blood supply to part of the brain is cut off.

**Tau** – proteins that stabilize microtubules. Tau accumulates in neurons, forming neurofibrillary tangles, leading to degeneration in a wide variety of disorders including Alzheimer’s disease.

**Telecare** – personal alarms and security systems which offer remote care of elderly and physically less able people.

**Triple negative breast cancer** – any breast cancer that does not express the genes for estrogen receptor (ER), progesterone receptor (PR) and HER2/neu.

**UK Department of Health and Social Care** – the UK Government department responsible for government policy on health and adult social care matters in England.

**Vascular dementia** – Vascular disease occurs where blood vessels are damaged and the supply of oxygen is at risk. If oxygen supply fails in the brain, brain cells are likely to die leading to a series of mini strokes (infarcts) and possible vascular dementia. Vascular dementia accounts for 20%-30% of all cases of dementia.

**World Health Organization (WHO)** – a specialized agency of the United Nations responsible for directing and coordinating matters relating to international public health, including for example Noncommunicable diseases.

## List of interviewees

**Dr Ricardo Allegri**, Head of Cognitive Neurology, Neuropsychology and Neuropsychiatry, Fundación para la Lucha contra las Enfermedades Neurológicas (FLENI)

**Dr Alireza Atri**, MD, PhD, Director, Banner Sun Health Research Institute, Senior Scientist, Alzheimer's Prevention Initiative, Banner Health, Sun City/Phoenix, Arizona, USA

**Kate Bingham**, Managing Partner, SV Health Managers

**Professor Henry Brodaty**, Scientia Professor of Ageing and Mental Health and Director, Dementia Collaborative Research Centre at the University of New South Wales

**Dr Doug Brown**, Chief Executive Officer, British Society for Immunology and former Chief Policy and Research Officer of the Alzheimer's Society

**Dr Jennifer Bute**, former General Practitioner. Visit Jennifer's website at: <http://www.gloriousopportunity.org/>

**Dr Maria Carrillo**, Chief Science Officer, Alzheimer's Association US

**Dr Christopher Chen**, Director, Memory Ageing and Cognition Centre, National University Health System, Singapore

**Francesca Colombo**, Head of the Health Division, Organisation for Economic Co-operation and Development (OECD)

**Dr Jeffrey Cummings**, Director, Cleveland Clinic at Lou Ruvo Centre for Brain Health

**Dr Rachelle Doody**, Global Head of Neurodegeneration, Roche

**Dr Serge Gauthier**, Director, Alzheimer's Disease Research Unit at McGill Centre for Studies in Ageing in Canada

**Dr Miia Kivipelto**, Professor in Clinical Geriatrics at the Karolinska Institute and senior geriatrician at the Karolinska University Hospital, Stockholm

**Professor Martin Knapp**, Professor of Social Policy and Director of the Personal Social Services Research Unit, London School of Economics and Political Science

**Professor Adesola Ogunniyi**, Professor of Medicine at University College Hospital, Ibadan

**Professor Martin Prince**, Professor of Epidemiological Psychiatry and Assistant Principal for Global Health, King's College, London

**Glenn Rees**, Chairman, Alzheimer's Disease International and former CEO, Alzheimer's Australia

**Professor Craig Ritchie**, Chair, Psychiatry of Ageing at the University of Edinburgh and Director, Centre for Dementia Prevention

**Professor Bart de Strooper**, Director, UK Dementia Research Institute

**Dr Kenji Toba**, President, National Centre for Geriatrics and Gerontology, Obu

**Professor Gordon Wilcock**, Emeritus Professor of Geratology, University of Oxford and co-founder, Alzheimer's Society UK



## **Alzheimer's Disease International**

### **About ADI**

Alzheimer's Disease International (ADI) is the international federation of Alzheimer associations throughout the world. Each of our 94 members is a non-profit Alzheimer association supporting people with dementia and their families. ADI's mission is to strengthen and support Alzheimer associations, to raise awareness about dementia worldwide, to make dementia a global health priority, to empower people with dementia and their care partners, and to increase investment in dementia research.

### **What we do**

- Support the development and activities of our member associations around the world.
- Encourage the creation of new Alzheimer associations in countries where there is no organisation.
- Bring Alzheimer organisations together to share and learn from each other.
- Raise public and political awareness of dementia.
- Stimulate research into the prevalence and impact of Alzheimer's disease and dementia around the world.
- Represent people with dementia and families on international platforms at the UN and WHO.

### **Key activities**

- Raising global awareness through World Alzheimer's Month™ (September every year).
- Providing Alzheimer associations with training in running a non-profit organisation through our Alzheimer University programme.
- Hosting an international conference where staff and volunteers from Alzheimer associations meet each other as well as medical and care professionals, researchers, people with dementia and their carers.
- Disseminating reliable and accurate information through our website and publications.
- Supporting the 10/66 Dementia Research Group's work on the prevalence and impact of dementia in developing countries.
- Supporting global advocacy by providing facts and figures about dementia, and monitoring as well as influencing dementia policies.

ADI is based in London and is registered as a non-profit organisation in the USA. ADI was founded in 1984, has been in official relations with the World Health Organization since 1996 and has had consultative status with the United Nations since 2012. ADI is partnered with Dementia Alliance International (DAI), a collaboration of individuals diagnosed with dementia providing a unified voice of strength, advocacy and support in the fight for individual autonomy for people with dementia.

You can find out more about ADI at [www.alz.co.uk/adi](http://www.alz.co.uk/adi)

Alzheimer's Disease International:  
The International Federation  
of Alzheimer's Disease and  
Related Disorders Societies, Inc.  
is incorporated in Illinois, USA,  
and is a 501(c)(3) not-for-profit  
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**Alzheimer's Disease  
International**

*The global voice on dementia*