

Shortlisted articles



Winner

Natasha Clarke, St George's, University of London

How artificial intelligence, and a cup of tea, could help diagnose Alzheimer's disease



I'd like to give you a quick task. How do you make a cup of tea? Describe it out loud. Whilst this could lead to some controversies (milk in first, or last?) it seems fairly simple. But what if I told you that this task could help diagnose Alzheimer's disease?

A person receives a diagnosis of dementia, of which Alzheimer's is the leading cause, every three minutes in the UK – that's one in the time it takes a kettle to boil. In Alzheimer's the hippocampus – the part of the brain we need to form and hold on to memories – starts to shrivel. Abnormal proteins build up in and around brain cells, killing them. Memories start to fade. And so does language.

This process is a slow one. We now know that by the time a person goes to their doctor with concerns about their memory, Alzheimer's could have been lying undetected for 10 years. Complex tests, brain scans and lumbar punctures can give a good indication if someone has Alzheimer's at this stage, but it's too late. How can we bring the diagnosis forward?

Brain scans are getting more advanced, but they're expensive. We need something that's sensitive to change, cheap and readily available – like a blood test. Something that will help us detect who is in the earliest stages of Alzheimer's, give medications sooner, and stop the disease in its tracks. Language. There's more information contained in language than we could ever imagine. The words we use can reveal our gender, how much power we hold, whether we're angry, sad or happy. It's a mirror to our inner selves, and very difficult to mask. And, language can also reveal signs of Alzheimer's.

Ground-breaking studies have found changes in what people say, or how they say it, years before they're diagnosed. President Ronald Reagan was diagnosed with Alzheimer's after

he left office, but showed signs that his brain was already changing in speeches made six years earlier.

Researchers could tell from essays written by nuns which of them would go on to develop Alzheimer's. Fans and critics alike panned Iris Murdoch's final book, which was later found to have used language very differently from novels written earlier in her career. She was diagnosed with Alzheimer's at 76.

This is what my research is doing. Finding clues in language that show the brain is changing. Building a method for detecting Alzheimer's before the memories start to fade, and the disease starts to spread.

The vast majority of us aren't presidents, nuns, or famous authors, though. We need to study the language of 'everyday people'. So, I'm analysing the language of volunteers diagnosed with early Alzheimer's disease or Mild Cognitive Impairment (MCI), where people experience some of the symptoms of Alzheimer's and are at a higher risk of developing it later.

I ask these volunteers to name as many animals as they can in one minute, to describe a picture, tell me a story and to describe how they make a cup of tea. I record their speech, and then search through the hundreds of features hidden in their language, and over one year follow them up to see how this changes.

But searching through these hundreds of features is like looking for a needle in a haystack. This is where Artificial Intelligence comes in. AI relies on Machine Learning, where a computer is given lots of data and learns something useful.

Take your spam email filter: it's been trained to recognise spam compared to real emails, by searching through the characteristics, or features, of each. Perhaps spam emails contain more website links? Or real emails tend to be longer? Once it's seen enough emails to learn what is different about the two groups, when you get a new email it knows what to look out for, and can banish that spam to the right folder.

This is how I will compare the language of my volunteers with Alzheimer's and MCI to the language used by people ageing healthily, and find the needle in the haystack of spoken words. I will train a computer to learn which features are important for identifying disease, so we know what signs to look for. For example, I'm looking at how common the words used by each group are. Is speech affected by Alzheimer's more predictable?

Blood tests look for biological markers of disease. I'm looking for a marker in language. Just like a blood test, it's sensitive to change, cheap and readily available, and could reveal Alzheimer's years before other symptoms start to show. With the help of AI, I hope that in the future diagnosing Alzheimer's will be quick, inexpensive and painless – as simple as making a cup of tea.

Runner-up

**Briet Bjarkadottir, Nuffield Department of Women's and Reproductive Health,
University of Oxford**

Stopping the conveyor belt – cancer and fertility



Jane is experiencing the worst day of her life. Her six-year-old daughter, Lily, has just been diagnosed with cancer. The doctor is describing the treatment plan for the next few months: several rounds of chemotherapy to hopefully kill off the cancer cells. He even mentions the possibility of a bone marrow transfer. All of this is way too much to take in – how can a little girl, who was happily playing on holiday a few weeks ago, be so sick?

The doctor then says something which makes Jane's head spin even more: the chemotherapy could make Lily infertile, and they need to decide whether to freeze one of her ovaries for the future.

A thousand different thoughts and questions race through Jane's head. The doctor mentioning Lily's future gives her mother hope that the treatment will work, but how can a child's fertility be in danger when she hasn't even gone through puberty? Is the danger to her future fertility great enough to warrant a potentially risky operation to remove one of her ovaries? What about Lily's own choice? She's much too young to grasp the idea of fertility; she won't understand why she needs to have the surgery. And what if she decides not to have children later in life?

This is a situation that I think no person should have to struggle with when confronted with a cancer diagnosis.

Infertility is a possible side effect of chemotherapy for both children and adults. While chemotherapy drugs are intended to kill cancer cells, most do not target these cells specifically and can cause collateral damage. Other cells that grow fast (like cancer cells do) can also be destroyed by the drugs; this is why people sometimes lose their hair.

Our reproductive organs, ovaries or testicles, can also be damaged by chemotherapy. But how are the ovaries affected?

It helps to think of the female reproductive lifespan as a conveyor belt. A girl is born with a supply of immature eggs; these are all the eggs she will ever have. From birth, groups of

immature eggs are constantly being added to the conveyor belt from the supply, and as the eggs move along they start to grow and mature.

The eggs are discarded at different points along the conveyor belt, and once a girl has gone through puberty a single mature egg will reach the end of the conveyor every month and be ovulated.

At any given moment, the conveyor belt contains eggs that are at different stages of growth, and immature eggs are only placed on the belt once space has formed at the end. The conveyor belt keeps running until the immature egg supply is exhausted and the woman goes through menopause.

Some chemotherapy drugs kill growing eggs, causing a new group of immature eggs to be taken from the supply and added to the conveyor. The supply itself is thought to be safe from the chemotherapy, as scientists think the eggs only become vulnerable once they start to grow. However, with each cycle of treatment, more and more eggs are removed from the supply and put on the conveyor until finally the egg supply is exhausted and the conveyor belt stops, causing infertility.

Freezing an ovary is the only way to protect the future fertility of someone as young as Lily. Other options exist for adult women, such as freezing mature eggs or embryos. However, all of these options are invasive and don't offer a guarantee of having a child.

My PhD is focused on finding a less invasive way to protect fertility in girls and women. At the moment, I'm looking at how exactly chemotherapy drugs affect the egg supply to see if they are truly unaffected if they haven't yet started to grow.

Next I will start testing compounds that have the potential to be able to prevent these immature eggs from growing, stopping the conveyor belt temporarily and protecting the eggs from damage by chemotherapy drugs. To do this I grow small pieces of ovarian tissue in the laboratory and study the effects chemotherapy drugs and compounds have on the eggs. This tissue comes from girls and women who have had their ovaries frozen before starting cancer treatment and have donated a small portion to medical research.

Once I find a compound that is able to stop the conveyor belt I hope it can be given to patients alongside chemotherapy treatment, and once the cancer treatment is finished, the conveyor belt would start up again and the patient would have normal fertility. In the future I hope that no one confronted with a cancer diagnosis has to go through the process Jane and her daughter Lily did, and can instead focus their energy on battling the disease.

Commended

Fraser Shearer, Centre for Cardiovascular Science, The University of Edinburgh

Keep calm and carry to term



In just a few weeks my first child is due. I have unbuilt furniture sitting in a wholly unprepared 'nursery' which is also my partner's office, a pram that I am still unsure about, sleep sacks that are apparently a thing babies use and, for someone who does not have breasts, I have a wealth of knowledge about breast pumps. This, however, pales in comparison to the list of things I do not have and the window for fulfilling that list is rapidly shrinking. Suffice it to say, my stress hormone levels are elevated.

As the man in this story, though, my stress hormone levels are nothing compared to my partner's. A woman's stress hormone levels rise throughout pregnancy and in the third trimester can be three times higher than pre-pregnancy.

This increase is normal, reflecting the fact that the baby needs stress hormones at the end of pregnancy to properly develop. But in pregnancy, as in comedy, timing is everything. In early pregnancy, stress hormones are so unwanted by the baby that it has a defence mechanism – a chemical that inactivates stress hormones. This ensures that even as Mum's stress hormone levels increase, baby stays in a zen-like state with stress hormone levels up to 10 times lower than Mum.

Unfortunately, the defence mechanism isn't completely impenetrable. If Mum's stress levels are increased early, maybe by something traumatic like a car crash, this can overcome the protection, exposing the baby to stress hormones.

Exposure to stress hormones at the wrong time can have a profound and long-lasting effect on the child. Starting with a lower birthweight and then an increased chance of lower IQ, depression and anxiety disorders continuing throughout their life. Mental health issues are thought to be the second leading cause of disability worldwide, so understanding how stress hormones might predispose us to poor mental health could help us treat it more effectively. To do this we need a way to look at how the developing brain is affected by stress hormones in pregnancy and for that we turn to mice.

The mice in our lab are almost completely normal but we have removed the defence mechanism from their brains. So, in the womb, any stress hormones that reach the brains of

the mice are not inactivated, they affect the brain all the way through pregnancy not just at the end. As adults, these mice have some memory problems and depression-like symptoms similar to those we see in humans.

It's amazing that in the vastly complicated process of brain development, a change as small as raising stress hormone exposure early can have such a big effect throughout the entire life of an animal.

The aim of my PhD project is to examine how this happens. What is different in the brains of these mice compared to normal mice? How could early exposure to stress hormones cause the symptoms we see in adults?

To try and answer these questions, I am taking brain tissue from our mice at different times during development. I look at how 'turned on' certain genes are in their brains compared to normal mouse brains. A big question for me, though, is which genes should I look at?

Some clues might lie in what we already know about mental health. In people with depression, a chemical called serotonin is often found to be decreased in the brain. In fact, this finding forms the basis of many of the treatments for depression. In the growing brain, serotonin is also very important, so it gives us a link between development and depression. Interestingly, in our mice I have found that a serotonin related gene is reduced, suggesting that the early stress hormone exposure might be affecting how serotonin functions. If serotonin isn't doing its job properly, that could change how the brain grows, another small change having a big effect.

This is far from the whole picture – brain development is a series of small things having big effects and stress hormones have wide ranging and varied effects – but certainly it suggests that serotonin may be altered long before symptoms of depression arise. Perhaps the problem in depression isn't low serotonin in the adult brain, but changes to how the brain grows after early exposure to stress hormones and serotonin is just the middle man.

It's impossible to predict stressful events and to protect pregnant women completely from exposure to stress, but by finding out exactly how it affects the baby we might be able to prevent the later life effects in the future. For now, if you know any pregnant women, make sure they are happy and safe; it's a small thing but it could have a big effect. And frankly, I can't stress that enough.

Sonja Klingberg, MRC Epidemiology Unit & Centre for Diet and Activity Research (CEDAR)

Obesity prevention: Learning to do no harm



“Our daughter doesn’t usually eat this for breakfast,” said the woman across the table from me. We were having breakfast together at a small lodge in South Africa, and I had just answered this fellow guest’s question about the topic of my PhD research. In hindsight, I probably shouldn’t have told her I study childhood obesity when we were having a nice conversation over a shared meal.

The woman’s 3-year-old daughter was eating sugary cereal, and I had not noticed this until I realised the mother’s embarrassment. If I had to guess, I would have assumed they were both a ‘healthy’ weight, and yet mentioning obesity had clearly alarmed the mother. Since then, I have been thinking a lot about how to promote health without promoting fears.

Childhood obesity is a significant public health concern but it is also a difficult one. I mean this both in the sense that it is genuinely difficult to address childhood obesity, and that it is a difficult topic to discuss. Nevertheless, we must discuss it because overweight, obesity, and related behaviours such as lack of sufficient physical activity, are associated with numerous severe health problems in childhood and beyond.

My research focuses on childhood obesity in South Africa where over half of adult women, and nearly half of adult men, are overweight or have obesity. Framing childhood obesity prevention in a way that can constructively engage parents rather than stigmatise them is a real challenge.

Particularly on social media, discussions around obesity prevention often suggest the problem is not the phenomenon of unhealthy excess weight gain but rather the people who ‘let’ this happen to them or their children. TV shows about obesity have names like Fat Fight and Biggest Loser. Even a recent Cancer Research UK campaign highlighting the link between obesity and certain cancers was criticised for being fat-shaming.

While the link to cancer is supported by scientific evidence, it is understandable that such a campaign would cause debate. It seems easy to forget that people's health, illnesses, appearance, and habits are not necessarily separate from their sense of identity. If obesity is part of who I am, how does it feel to hear that who I am can cause cancer?

It is well-documented that many health problems, including overweight and obesity, are patterned by society's existing inequalities. Diagnoses often come with stigma attached, and stigma in itself can be harmful to health and well-being, as well as disadvantage people in many other ways. Thus, we ought to consider how research and health promotion efforts may inadvertently contribute to such harm. We should also not assume that weight-related stigma means the same thing across cultures and settings.

In my research, I am learning to approach these topics through interviewing parents of preschool-age children in South Africa about their perceptions and circumstances. How do parents interpret health and healthy behaviours? What constrains them, and what might help them? Such insights will help design childhood obesity prevention efforts that can hopefully resonate with the lived experiences of families.

As part of my PhD research, I have also reviewed childhood obesity prevention programmes in different African countries to understand what works and what doesn't. I have not come across any studies that have found fat-shaming, parent-blaming, humiliation, or any kind of judging, an effective way to address overweight and obesity. Nevertheless, I can see how people might expect shame or fear to motivate healthy habits and weight-loss.

Behavioural science has helpfully identified some conditions that seem to define how well fear-arousing health messages work. Firstly, people need to believe that changing their behaviour would actually make them healthier or safer. Secondly, people need to believe in their own ability to change their behaviour. Losing weight in the longer term is notoriously difficult, and so evoking people's fears without also encouraging them to think they can do something about it is unlikely to work.

So, while I don't yet know what exactly will work to prevent childhood obesity in South Africa, I do know this: parents may have different views on what is healthy and what is best for their children but we should stop trying to scare them into changing their views and habits. It's not nice, and it probably won't work.

Nuzhat Banu Ashra, University of Leicester, Department of Health Sciences

Pregnant women: urine good hands



What is the most frightening part of pregnancy?

Most women would probably answer labour and birth. There is the prevailing fear of not knowing what to expect, if it is the first time, and knowing exactly what to expect if it isn't. Understandably, the not so small matter of propelling a pumpkin-sized human out of a comparatively smaller receptacle is a daunting prospect. After going through the experience twice already I don't think I'd look forward to a third with anything but a sense of trepidation. The pain, the sweat, the tears... We can agree then, that the prospect of childbirth is terrifying.

But what about the women who are terrified they'll never make it that far?

The women who may or may not struggle to conceive, but most definitely struggle to carry their precious cargo to term. For these women the most frightening part of pregnancy is the first trimester. Those initial 12 weeks, during which the risk of miscarriage is at its highest, can elicit a rollercoaster of emotions and ostensibly there is nothing to be done to prevent a miscarriage.

With the squeeze on healthcare resources and limited midwife contact during pregnancy, a detailed picture of pregnancy progression is difficult to establish. An isolated occurrence of miscarriage is not thought to adversely affect a woman's chances of conceiving in the future, due to the frequency with which pregnancy loss occurs. In fact, it is estimated that 15% to 20% of clinically confirmed pregnancies end in miscarriage before week 13. This excludes spontaneous losses which occur before the mother even becomes aware of conception.

Arbitrarily, suffering three miscarriages moves a woman from the low to high risk category, at which point monitoring contact may increase. However, vaginal/ultrasound scans will still not usually be offered prior to the sixth week of pregnancy. After six weeks a scan may be offered, but only at the discretion of the healthcare professional. So with no tangible 'proof' of a sustained pregnancy throughout the weeks prior to the 12 week scan, prospective mothers are left to steep in their anxiety.

Certainly the high cost involved in offering 'extra' scans, as well as the increasing demand for such appointments, means that additional scans may not be the most cost-effective way of monitoring high risk pregnancies. So, is there another less resource intensive way in which healthcare professionals may monitor a pregnancy in those early weeks?

Well the answer is in the... urine?

Pregnancy is confirmed by testing the level of a particular hormone in a woman's urine. So, whether it is two blue lines, 'pregnant' or a little plus sign, the positive indicator means there is at least 25 mIU/mL of human chorionic gonadotrophin (hCG) present in the urine. In a healthy pregnancy the level of this hormone typically doubles every 48-72 hours, before plateauing and decreasing in the second and third trimesters. This makes hCG an appropriate hormone for use in monitoring progression in early pregnancy, and it's as easy as one, two, wee. Ahem.

This is where my research project comes in. I will be using data provided by SPD Development Company Limited to develop a statistical model that can predict a woman's risk of miscarriage. By including the repeatedly measured hCG values in the model, I will be able to look at how the changes in hCG can be used to track the progress of pregnancy. Not only will I be able to use this data to model hCG, I can look at different maternal characteristics like age or the number of previous miscarriages to see whether this contributes to an increased or decreased risk of miscarriage.

The emphasis of my research is on developing a program which outputs individualised predictions. The model which best describes the relationship between hCG and miscarriage can form the basis of an application, which allows hCG values and maternal characteristics to be inputted to give a current risk of miscarriage. This tracking of hCG in real time means medical intervention can be arranged immediately, whether this is of a physical or psychological nature.

We are now a society which has come to value control over our own healthcare. We want to be active participants in our healthcare journey, rather than being relegated to observers on the side-line. An app which hands women a measure of such autonomy has the potential to have a powerful effect on their mental well-being during pregnancy, by allaying the helplessness and anxiety they may feel.

Inevitably, intervention will not prevent an early miscarriage for every woman, but we can, with continued research, begin to lift the shroud of mystery surrounding the issue. And with more information out there about miscarriage, we are projecting the right message to pregnant women.

You're in good hands.

Helen Parker, University of Edinburgh

Coughs and sneezes spread drug-resistant diseases



During World War II the Ministry of Health released posters warning citizens that *coughs and sneezes spread diseases*. These posters were designed to keep the nation “fighting fit” but they would have been just as pertinent two decades earlier. In 1918, Spanish Flu was one of the worst natural disasters in history, killing 3 to 5% of the global population.

One reason for its deadliness is that a person only needed to inhale a thousand virus particles to become infected. We call this number the disease’s *infectious dose*. A single sneeze from someone infected could contain hundreds of thousands of virus particles. Why the history lesson? Because, as the saying goes, those who do not learn from history are doomed to repeat it.

Tuberculosis is a lung infection spread through coughs and sneezes and has an infectious dose of around three bacteria. It’s little wonder, then, why one third of the global population carries some form of tuberculosis. That’s over 2 billion people. My research is on aspects of tuberculosis that could lead to a devastating pandemic.

We haven’t yet reached this pandemic because of two main factors. The first is that many people are either immunised or have access to antibiotics. The second is that while some diseases, like the flu, attack the infected person aggressively, tuberculosis plays a longer game.

When a few inhaled bacteria infect an immune cell in the lung more immune cells swarm to the infected one, isolating it from the body but unable to eliminate it. This forms a structure called a granuloma. If the granuloma manages to contain the infection we call it latent.

Latent tuberculosis is symptomless and is what most of those 2 billion people have. If the infection isn’t contained the tuberculosis becomes active and without treatment the chances of death are over 70%. One in ten people with latent tuberculosis will eventually develop active tuberculosis, sometimes years after initial infection.

Tuberculosis research is usually carried out by biologists in a lab, but I’m a physicist and my lab is my laptop, a pen, and some paper. By starting with what we already know from experiments, I write equations for each relevant biological event, such as the rate of bacteria replication and immune cell death. Together, the equations form a mathematical model that simulates how a granuloma behaves. It shows us how the balance of bacteria, immune cells, and other factors lead to a granuloma succeeding or failing to contain the infection.

Typically, doctors treat the infection with antibiotics. However, when antibiotics are given there is some probability that bacteria will develop resistance to them. Because of this there

is a new form of the disease emerging. And it's happening quickly due to widespread incorrect use of antibiotics. It's called multidrug-resistant tuberculosis – tuberculosis that doesn't respond to our current antibiotics but spreads and operates as insidiously as before.

Since 1984 no new antibiotics have been developed, which means that we are at risk of facing a deadly disease that could proliferate the world over and be largely untreatable.

The big aim of my research is to add the role of antibiotics to my model because I want to know how best to approach this problem. How do we treat people in a way that doesn't allow resistant tuberculosis to develop? Giving antibiotics too early or too late, in too low a dose or too high could all shift the outcome in our favour or the infection's.

Tuberculosis is a disease from the Neolithic age, so it would be spurious to claim my model replicates all its intricacies. In fact, intricacies often make problems less tractable. I reduce the granuloma to its fundamental parts to model it. This may seem like a step backwards, but what I lose in detail I gain in clarity – seeing the wood for the trees is a saying that springs to mind.

For example, I may find that by ignoring interactions of the granuloma with other cells in the body, subtle yet key interactions within the granuloma become apparent. And if so, can these be exploited for better medical treatment? Partnering biology with physics may provide insights we couldn't get from either discipline alone.

Mathematical modelling of biological systems is relatively young, but it does have enormous potential. Other drug-resistant diseases are on the rise. The World Health Organisation predicts that by 2050 death from infection will kill more people than cancer. Breaking new ground in drug-resistant tuberculosis modelling may help to progress the understanding of these diseases as well. *Coughs and sneezes spread drug-resistant diseases* isn't as catchy as its war time predecessor; but it's far scarier. When the stakes are this high, knowing your opponent is the smartest move of all.

Stephanie Louise Cumberworth, MRC University of Glasgow Centre for Virus Research

The Zika virus and the 'Brain in a Dish'



Mosquitoes. You might have encountered these bothersome bloodsuckers whilst enjoying a hard-earned holiday. If you are lucky, a few days of a red itchy bump will be the most you have suffered at the hands of a mosquito bite. However, over 1/3 of the world's population is at risk of severe infections spread by mosquitos.

One such infection is caused by the Zika virus. The virus rose to media fame in 2016 following an outbreak starting in Brazil which caused devastating, never before seen complications in new-borns. Previously, the Zika virus was thought to cause fever and a rash in 1/5 patients it infects. Now the virus has been linked to some babies being born with abnormally small heads and underdeveloped brains, amongst other neurological symptoms. I am part of a biological super team of neuroscience and virus experts who are investigating the cause of these new symptoms using a 'brain in a dish'.

Rest assured, the 'brain in a dish' is less Frankenstein-ian than its name suggests; nor is it a strange delicacy served up in a bowl like my friends imagined. It isn't really a brain at all. The 'brain in a dish' is actually a collection of different building blocks called cells, interacting with one another similar to how they would in the brain inside a specialised culture dish.

Part of my PhD involves using the 'Brain in a dish' to find out how the Zika virus affects these brain cells to try and answer the question: what does the Zika virus do to the brains of infected babies?

To get 'the brain in a dish' ready for experiments, we let the cells grow to the developmental stage that is representative of a new-born baby. As each cell type plays a different role in the brain, our first step was to find out which of the cells could be infected with the Zika virus; this might give clues as to what is causing some of the new neurological symptoms.

After infecting the 'brain in a dish', I use a chemical to 'kill' the virus and preserve the cells so that I can study them closer. Much, much closer in fact.

Next comes my favourite part: illuminating the 'invisible'.

Individual cells are so small that we can't see them with the naked eye. Viruses can be 1000x smaller than some cells, making them impossible to see without the right tools. To explore the microscopic landscape of the 'brain in a dish' I use specific labels against each cell type and the virus, which fluoresce my chosen colour when excited by a particular wavelength of light. Using a powerful microscope, I can then zoom in to reveal a rainbow of data.

Similar to a game of spot the difference, myself and a team of researchers scoured through images taken with the microscope examining each cell, noting what it was, if it was infected and if it was dying. The only difference being the average game of spot the difference takes minutes, ours took weeks. It wasn't long before I saw the patterns of cells everywhere I looked.

Our results showed that the main target for Zika virus infection was the oligodendrocyte. To understand the job of an oligodendrocyte, I first need to introduce the neuron. Neurons control every bodily process by sending messages from the brain along 'wires', called axons, to distant places in the body. Oligodendrocytes speed up this messaging service by providing a protective coat called the myelin sheath. The myelin sheath acts like the plastic coating around wires, it provides insulation and allows the wire (or axon) to transmit signals more efficiently.

Knowing that the Zika virus infects oligodendrocytes, our attention turned to the protective coat they provide axons – the myelin sheath. We found that infection with the Zika virus actually destroys the myelin sheath in the 'brain in a dish'. Not only that, we also saw that axons (the wires of the brain) were damaged too. Under the microscope what once appeared as infinite branches of communication, turned into a smattering of debris during infection.

So what does this mean for an infected baby's brain?

At birth, the axons in a human baby's brain aren't all fully covered by the myelin sheath. In fact, this process happens late in pregnancy and occurs all throughout childhood, into early adulthood. If the Zika virus affects the development of the myelin sheath in a new-born, it is possible that more problems might occur later in life. It is my hope to understand more about this myelin loss in the remainder of my PhD, so eventually it may be stopped. For every wire needs an insulating coat.

Kevin O’Gallagher, King’s College London, The James Black Centre

Heart-Beets



Heart doctors like me have been grappling with a serious problem for some time. About half of all patients we see with failing hearts have a condition which has a death rate as bad as many cancers. Many of our established heart drugs have been used in an attempt to treat this disease, but so far none have been effective. However, there is now a beacon of hope on the horizon: surprisingly not in the form of a fancy new drug or novel operation; rather, it is the humble beetroot.

‘Heart failure’ was traditionally thought to be caused by the heart muscle not pumping vigorously enough – a ‘weak’ heart. We now know that about half of patients with heart failure in fact have normal pumping function; the issue is that their hearts are too stiff and cannot relax well enough after each squeeze. This is called Heart Failure with Preserved Ejection Fraction.

Patients with stiff hearts get breathless very quickly when exercising. This is because the pressure inside the heart rises very quickly during exercise, something that does not happen in healthy hearts. This inability to exercise has a significant impact on patients’ quality of life. In severe disease the breathlessness becomes so severe that it occurs at rest; these patients need to be admitted to hospital for treatment. Overall, 1 in 5 patients with stiff hearts die within 3 years.

And this is where beetroot plays its part.

Beetroot is rich in a nutrient called dietary nitrate. When we eat beetroot or drink beetroot juice, our body converts the dietary nitrate into a chemical called nitrite. I have already performed a preliminary study to show that when we give nitrite directly to patients with healthy hearts, it decreases the pressure inside the heart. This raises the tantalising possibility that patients with stiff hearts could be cured simply by eating more beets!

I am currently carrying out two MRC-funded studies to test the effectiveness of nitrite and beetroot juice in patients with stiff hearts.

First, I am testing whether giving nitrite directly to stiff hearts improves relaxation and stops the abnormal pressure rise that we see on exercise. I place a special wire in the patient's heart to measure changes in heart function, including relaxation. I then give the patient a dose of nitrite directly to the heart while they exercise on a specially-adapted exercise bike which can be used in our operating room. Although it is rather novel to ask patients to perform bicycle exercise while lying flat on their backs with wires and tubes in their heart (all while they are awake), this research method, in addition to being safe, is the most accurate way of obtaining recordings of heart function.

Secondly, I am about to commence a formal clinical trial of beetroot juice in patients with stiff hearts. I will give these patients beetroot juice shots to drink every day for two weeks. Before and after the treatment period, the patients will complete an exercise test, whilst I take ultrasound images of the heart to measure its pumping function and relaxation levels.

Patients will undergo two courses of beetroot juice treatment. In one of the two-week periods, they will take normal beetroot juice ("active"). In the other they will take a specially-produced version of beetroot juice which doesn't have any dietary nitrate in it (the "placebo"). Neither I, nor the patients, will know which type of beetroot juice they are taking at any given time. Furthermore, the order of the treatment periods (active followed by placebo versus placebo followed by active) will be completely random. The scientific validity of the research is therefore ensured.

Why the need for beetroot juice, rather than focusing simply on nitrite itself? To develop an oral form of nitrite would require efforts over many years to produce a tablet which could be provided to patients by prescription. In contrast, beetroot, as a simple vegetable, does not need a prescription. Beetroot juice therefore represents the quickest, simplest and most cost effective (if not, for many, the tastiest!) way for patients with stiff hearts to access treatment. Assuming that I am able to prove that beetroot juice is effective in treating patients with stiff hearts, it will provide cardiologists and patients alike with a brand new treatment for this prevalent and presently dangerous condition.

Emily Granger, The University of Manchester

Confounded by medical data: can we trust what researchers say?



The more ice-creams are bought, the more murders occur. Does this imply buying ice-cream makes you more likely to murder or be murdered? I've heard the expression "I'd kill for an ice-cream" on more than one occasion, but taking this literally is a bit extreme. Perhaps committing murder makes one crave ice-cream, I wouldn't know. Realistically, something else is probably causing an increase in murders and ice-cream purchase: the weather.

When it's cold, people are less likely to eat ice-cream and more likely to stay inside their warm homes, not getting murdered. In hot weather, as well as eating more ice-cream, people spend more time outside, socialising with others and getting into all sorts of sticky situations which could lead to murder. Weather, in this case, is a confounder.

A confounder is a factor which confuses (or confounds) an association between two other factors. Admittedly there isn't a huge risk of misunderstanding in the ice-cream example. Not many people would jump to the wrong conclusion and start campaigning against ice-cream to save lives. But in medical research, confounders are a huge problem.

Suppose you are a researcher trying to combat heart disease. In a study of the effects of vitamin supplements, you find that far fewer people taking vitamins have heart related problems compared to those who don't take vitamins. So you conclude that supplementing your diet with vitamins lowers risk of heart disease. Many researchers in the 90's conducted studies like this and came to the same conclusion.

But we were fooled. It turns out that people taking vitamins were more likely to make other healthy lifestyle choices. They ate more fruit and vegetables, found motivation to exercise regularly and resisted drinking heavily on the weekends. It was these lifestyle choices that lowered risk in heart disease, not the vitamins. The lifestyle choices were confounders causing confusion. This is still a problem today. When analysing medical data, confounders make it difficult to obtain trustworthy results; a frustrating problem given that we live in the age of big data.

Existing medical databases are huge. We have access to billions of hospital admission records, patient care records, disease registries and much more. Researchers want to analyse this data to understand the causes of disease or to assess how effective various treatments are for patients. But we can't rely on results obtained using this data, because it is rich with confounders. We need a solution. My research involves a potential solution; a statistical tool called a 'propensity score'.

A person's propensity score is the probability that they receive the treatment of interest given their personal characteristics. When investigating the link between vitamins and heart

disease, a person's propensity score would be the probability that they take vitamins given their age, gender, diet and so on. Propensity scores *can* be used to eliminate confounders, but we never know the true values. We have to estimate propensity scores and if our estimates are wrong, they won't work. Currently, there is no way of knowing if our propensity score estimates are right or wrong, so it is still difficult to trust results obtained using them. To solve this, I am developing a propensity score test that researchers can use to check if their estimated propensity scores are correct.

I've started by considering existing statistical tests and modifying them to be appropriate for propensity scores. These modified tests are the candidates for my propensity score test. I compare the candidate tests using data that I've simulated. The advantage of simulating my own data is that I will know the correct propensity score (unlike in real data).

So I can analyse my data using the correct propensity score and an incorrect one to see which candidate test is best at identifying when the correct propensity score was used. Making these comparisons across a wide range of simulated data scenarios will ensure that the propensity score test I choose is widely applicable to real medical data.

The propensity score test is going to help solve our confounder problem. Researchers will be able to use the test to show that they have eliminated confounders and that their results can be trusted. When we can trust the results obtained using medical data, the potential impact on patient healthcare is vast, spanning across all areas of medicine.

Policy-makers will be able to use the information obtained from trustworthy results to improve population health and transform patient care, providing better outcomes for individuals and society as a whole. Plus, we can enjoy eating ice-cream without being concerned that it will cause us to go on a murderous rampage.

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Immune cell diet, cure for asthma?



You are on a holiday with a good friend walking along a path enjoying the stunning view and the beautiful scenery along the river. Suddenly, your friend starts coughing. He might have inhaled dust from the dry pathway. You stop to give him the water bottle from your backpack. The water does not help the coughing. He wheezes every time he breathes and you start panicking when you see that his face is getting paler and paler.

"I cannot breathe!" he says while wheezing.

You want to help him but you do not know what to do. What does he need? Do you have to call an ambulance? As the coughing and wheezing does not stop, you decide to call the ambulance. With shaking hands, you type in the number and call the paramedics.

It does not take long until the ambulance arrives and your friend is transferred to the nearest hospital where a team of doctors is waiting for him. After treatment, one of the doctors tells you that your friend has had a severe asthma attack but he is feeling better now. He must have inhaled some sort of trigger that led to inflammation in his airways which made his airway muscles contract.

As a consequence, his airways became narrowed making it difficult to breathe. The doctors were able to give him some medication that relaxed his airways making it easier to breathe again. Unfortunately, there is currently no permanent cure for asthma and your friend was lucky he did not die.

To find new, more effective treatments, it is important to understand the underlying mechanisms of asthma. When breathing in, one of the first cell types that greets the inhaled particles are called 'macrophages'. These are immune cells that love to eat up particles in the inhaled air by a process called 'phagocytosis'. Then, they decide if the particles they ingested are harmful or not.

As well as enjoying a good meal from time to time, macrophages are also chatterboxes who enjoy talking with other cell types in the lung, such as the ones lining your airways. They tell them about the things that they find. Macrophages inform these other cells if the particles in the inhaled air are harmful or not. The macrophages recognize that if the particles in the air inhaled are not dangerous, nobody needs to over-react.

However, if the macrophages think the particles are dangerous, it's time to call in reinforcements. Regarding your friend who had an asthma attack, the macrophages made a mistake. For some reason they thought that a harmless pollen particle was dangerous, and told all the other cells to panic. To understand asthma, we need to first understand why sometimes macrophages give this wrong information to the surrounding cells.

Macrophages that spend all their time nattering to other cells and gobbling up inhaled particles need lots of energy. They can use different mechanisms to produce the required energy depending on what the energy is needed for and also on what kind of pathogen the cell encounters. In order to react to harmful particles in the inhaled air, it needs to produce energy as fast as possible. For this purpose, macrophages rely on glycolysis, a process that quickly converts the sugar these cells use into energy. However, the yield of energy is very small. To produce high amounts of energy macrophages can turn on a different mechanism, called 'TCA cycle'. This mechanism takes longer but it results in much higher amounts of energy.

The aim of my PhD project is to study the way how the macrophages produce energy. This process of metabolism seems to be different in asthmatic and non-asthmatic people. Therefore, it is a major goal of my research to characterize which steps in the metabolism process differ and how they differ. To do so, macrophages of asthmatic and non-asthmatic patients are washed out of the lungs by so called 'brochoalveolar lavage'. Subsequently, these macrophages are compared regarding the mechanisms they rely on to produce their energy to function as an effective defense against pathogens in the inhaled air.

After finding and analysing potential differences in the metabolism of macrophages of asthmatics and non-asthmatics, it can be tested if these distinctions are the reason why the macrophages of an asthmatic react to particles in the inhaled air even if no reaction is needed.

The subsequent step will be to test if drugs modulating the pathways of the energy production in macrophages can effectively treat asthma. Ultimately, if a drug like this could be developed then this would prevent people having severe asthma attacks. This drug would help to prevent that your friend gets another asthma attack and to avoid that he has to spend his holidays in hospital.