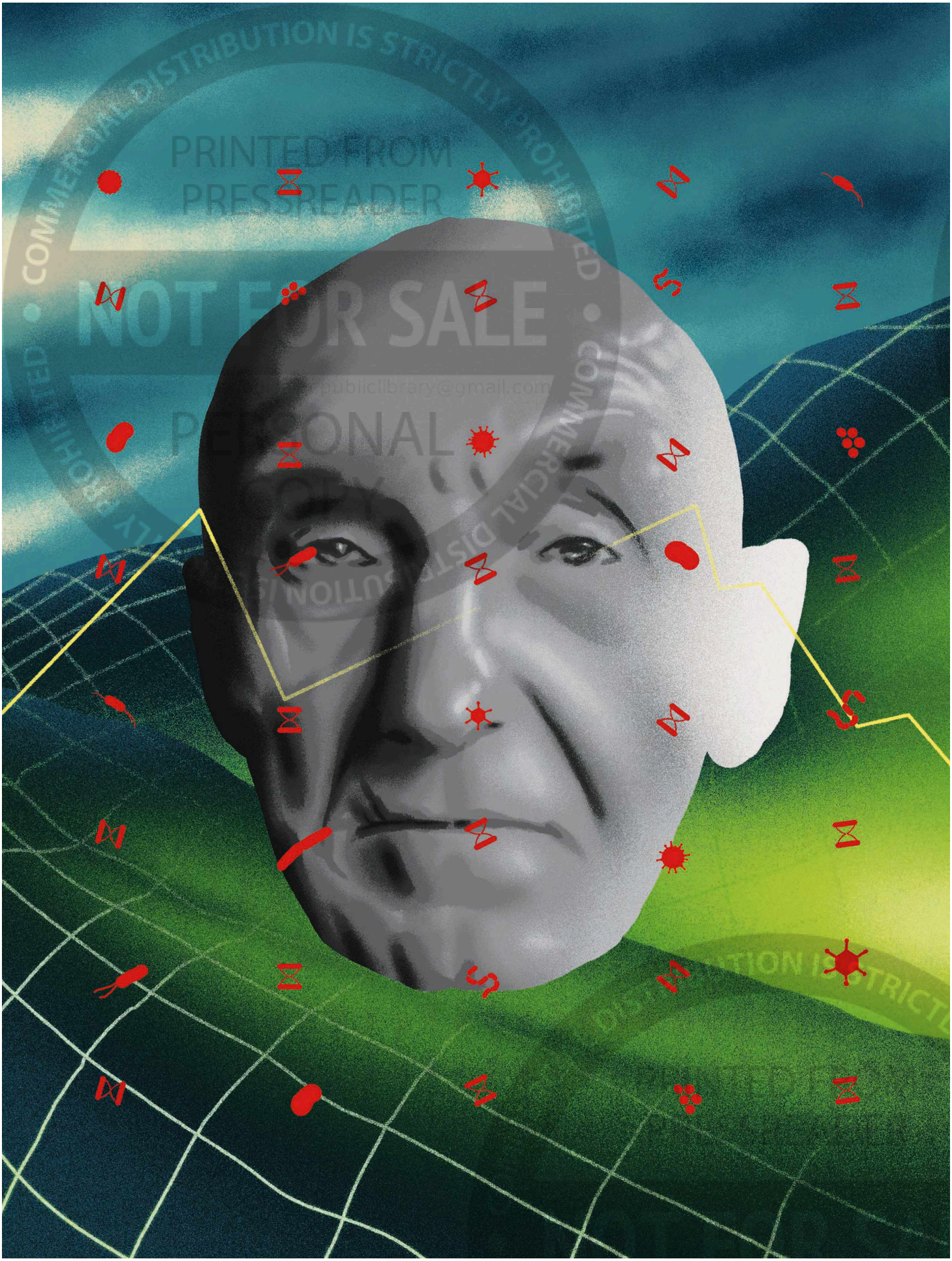
- Digestion



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GUT REACTION

Scientists have been telling us for years that if we love our gut bacteria, they'll love us back and help us with everything from easing digestion to fighting disease. Now, new research suggests that our microbiomes can even help us resist the effects of ageing... if we treat them right

by DR HELEN PILCHER

Take a stroll through the supermarket and you'll find plenty of products stuffed with 'friendly bacteria.' Bacteria – the good guys! Chug them down and they'll help to look after you. We're used to the idea that our guts are teeming with microbes and that they can be topped up with fancy yoghurts. We give the bacteria somewhere to live and, in return, they help us to digest our food. It's a mutually beneficial, two-way street.

Only this cosy relationship isn't quite what it seems.

Hidden among their ranks is a dark cabal of interlopers. To call them 'unfriendly bacteria' would be an understatement. These are microbial hell-raisers and as we get older, they slowly start to wreak havoc.

ILLUSTRATION: BERNARD LEONARDO

"OUR GUT BACTERIA PLAY A KEY ROLE IN MANY NEGATIVE ASPECTS OF AGEING"

It turns out that our gut microbes aren't always the good guys we think they are. A growing body of evidence suggests that our gut bacteria play a key role in many of the negative aspects of ageing, such as disease, frailty and the faltering of the immune system. But all isn't lost. We may not be able to stop getting older, but as we learn to harness the power of the microbiome, we can use it to help us age better and avoid ill health.

GOOD BIOME, BAD BIOME

The gut microbiome is made up of over 100 trillion microorganisms, including various bacteria, viruses and fungi. Round them up and they would weigh about as much as a hamster. If you leave them be, though, they can be found throughout the entire length of the human gut, all the way from the mouth to the anus. →

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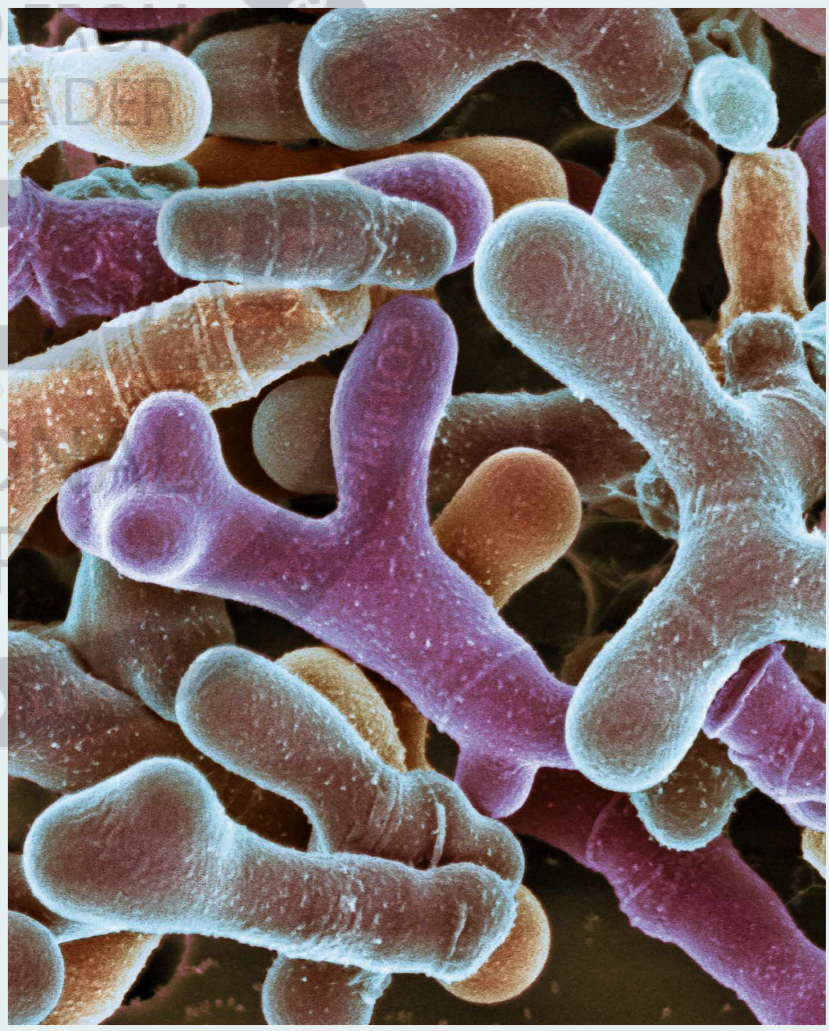

→ Established at birth, the gut microbiome develops through early childhood. Its makeup is a reflection of what we eat, where we live and what we do. Colonies of bacteria are laid down – some good, some bad, others somewhere in between – that then remain broadly stable for decades.

During this time, the good guys predominate. They assist us by breaking down dietary fibre, which releases energy that we can use, and by making nutrients, such as vitamin K and folate. In addition, they help to keep the bad guys in check and prevent them from making us sick.

So far, so good. But then, from age 50 or so onwards, the composition of our gut microbes starts to change.

The good guys, such as *Roseburia* and *Bifidobacterium*, start to decline, while the bad guys, such as *Escherichia* and *Streptococcus*, start to increase. Overall, there's a loss of diversity. "The composition and the function of the microbiota start to change," says Dr Aimée Parker from the Quadram Institute in Norwich.

Compare the gut microbiome of a group of 80-year-olds with a group of 18-year-olds and they look very different. There are also differences between the gut microbiomes of healthy older adults and older adults who suffer from frailty, thinning bones, Alzheimer's disease and Parkinson's disease.

Studies have highlighted distinct microbial signatures associated with type 2 diabetes, cardiovascular disease and colorectal cancer – all diseases that become more common from mid-life onwards – but, for a while, no one knew whether these features were a cause or an effect. Does the microbiome drive ageing and age-related disease, or does ageing and ill health lead to changes in the microbiome?

THE EFFECTS OF AGEING

The answer, we now realise, is both. Age-related changes to the gut have an effect on bacterial composition, as do illness, poor diet, physical inactivity and the use of certain medicines, which all become more common as we get older.

"COMPARE THE GUT MICROBIOME OF A GROUP OF 80-YEAR-OLDS WITH A GROUP OF 18-YEAR-OLDS AND THEY LOOK VERY DIFFERENT"

ABOVE A coloured electron micrograph of *Bifidobacterium animalis*, a probiotic bacteria found in the large intestine

TOP RIGHT Mucin is produced by the colon

RIGHT The abundance of certain strains of *Escherichia coli* (*E. coli*) bacteria found in our guts increases with age

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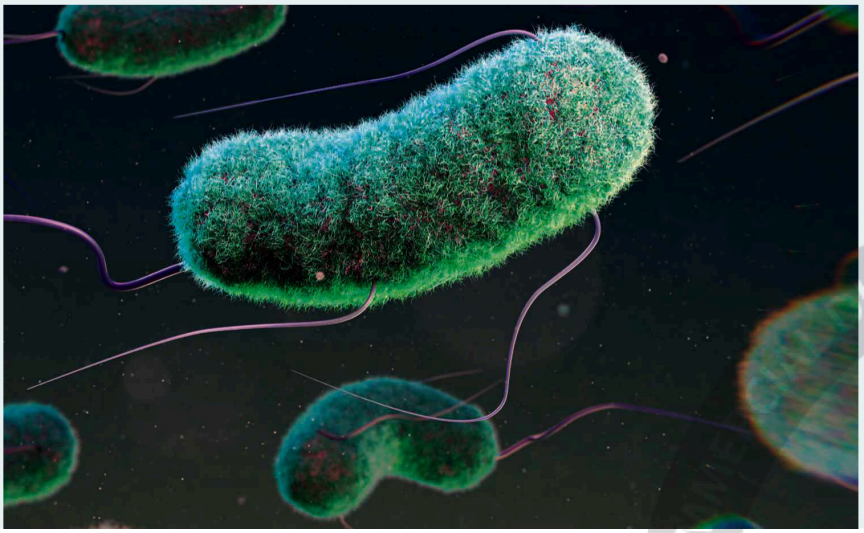

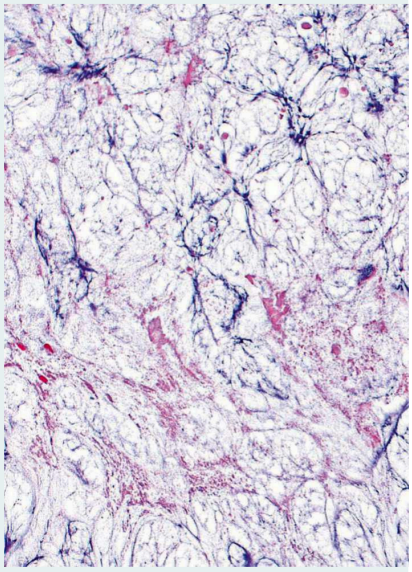

The relationship goes in the other direction too, though. Alongside the various factors that we already know more about, such as genetics and lifestyle choices, the gut microbiome is one of the things that actually drives ageing.

We've arrived at this knowledge mainly thanks to information gathered through experiments known as 'Faecal Microbial Transplants' (FMT) or, more colloquially, 'poo transplants.' They do exactly what the name suggests. Faeces are teeming with gut microbes. In carefully monitored studies, faeces from old animals can be transferred to the guts of young animals, which are then monitored over time.

When the experiment is performed on flies, it shortens their lives. When it's performed on mice, the animals show signs of memory impairment.

Effects can be seen throughout the body, at the level of molecules, cells and even whole organs. Parker has shown that young mice who receive 'old' microbes, develop age-related changes in the gut, eyes and brain. A key protein required for vision becomes depleted, while levels of inflammatory markers in the brain increase. →

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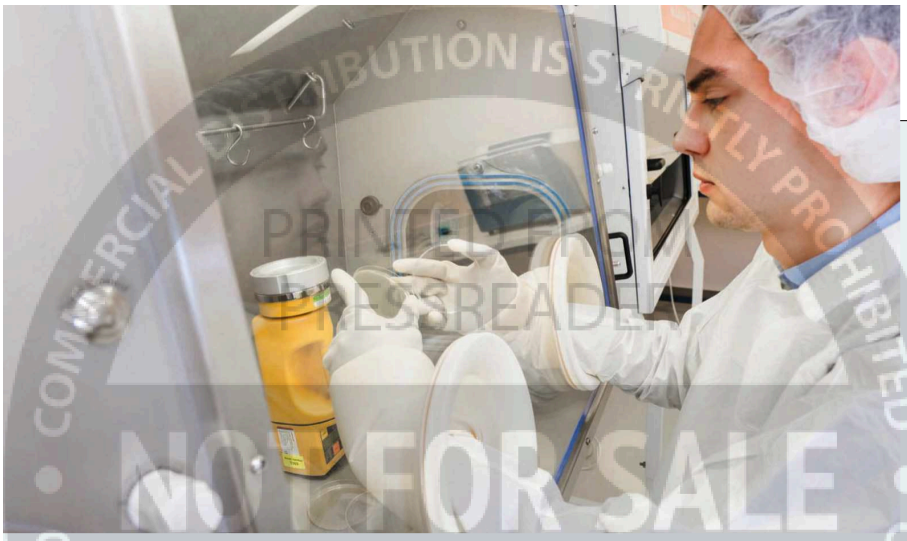



→ "What happens in the gut, doesn't stay in the gut," says Parker. "It affects the rest of our bodies."

The picture that now emerges is that as the 'bad guys' start to take over, the gut wall starts to deteriorate. 'Friendly bacteria' stimulate the production of a slimy protein called mucin, which helps to protect the lining of the gut. With less mucin, the lining becomes damaged. The gut becomes inflamed and leaky. Microbes and the products that they make, leach into the body and are carried to distant places in the bloodstream.

This doesn't go unnoticed by the immune system, which springs into action, triggering a chronic, low-level inflammation known as 'inflammageing.' This isn't good. Inflammageing is widely recognised as a sign, or 'hallmark', of ageing, which plays a role in the development of many age-related diseases, including cancer and cardiovascular disease.

In addition, the immune system itself becomes aged. Microbial products reach the thymus, a plum-sized gland that sits above the heart and is part of the immune system. It makes specialised immune cells, called T cells, which help the body fight infection. The thymus is known to



TOP LEFT Research into faecal microbial transplants has produced vital information on how the microbiome can affect the ageing process

ABOVE LEFT A petri dish containing cultures of donor stool samples being tested ahead of a faecal microbial transplant

LEFT Syringes containing a stool solution are prepared for a faecal microbial transplant to treat patients with colon infections

SCIENCE PHOTO LIBRARY X2, GETTY IMAGES ILLUSTRATION: BERNARD LEONARDO

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"EVEN IF THE SLIDE TOWARDS MICROBIAL DISORDER CAN'T BE ENTIRELY PREVENTED, IT CAN CERTAINLY BE SLOWED"

shrivel with age, but Dr Niharika Duggal from the University of Birmingham has shown that this shrinking may be driven by the ageing and increasingly disordered microbiome.

"We think this could be contributing to the senescence we see in your thymus as you get older," she says. Indeed, Duggal has shown that adults who have leakier guts also have older and more exhausted T cells.

SLOWING THE DECLINE

So, how do we protect ourselves from this microbial mayhem? "The good news is that the microbiome is very malleable," says Duggal. Even if the slide towards microbial disorder can't be entirely prevented, it can certainly be slowed, which is almost as beneficial.

To see the effects of this, researchers have performed 'reverse' faecal transplants, where the microbes of young mice are manoeuvred into the guts of old mice. The gut becomes less leaky, inflammation is reduced and the immune system shows signs of becoming healthier. Hallmarks of ageing in important organs, such as the eyes and brain, also decrease. The older mice even show improvements in cognitive function and their memories start to improve.

Buoyed by these findings, researchers at the Quadram Institute in Norwich are setting up an FMT facility to trial faecal transfers for people. Presently, the technique is used in the clinic, but only for the treatment of hard-to-shift *C. difficile* infections. Patients receive transplants from healthy, screened donors, which are given either by colonoscopy, endoscopy or a tube that goes up the nose and down into the stomach. The procedure is highly effective, with a success rate of around 85 per cent.

If further pre-clinical studies go well, Parker hopes to test the effects of FMT on ageing in humans. "We'd like to see if there are differences in measures such as frailty, visual ability and cognitive performance," she says.

For many people, however, even the thought of a faecal transplant can be butt-clenching. So, researchers are developing alternate methods, including freeze-dried faecal transplant capsules, which, they hope, will be easier to swallow.

Another potential approach to combat the worst effects of ageing, is to boost levels of the 'good guys' by taking prebiotic and probiotic supplements. Prebiotics are fibre-based products that promote the growth of healthy gut bacteria, while probiotics contain the 'good guys'.

Lots of people buy the supplements off-the-shelf and swear that they feel better for taking them, but their ability to influence ageing in the long term is only just starting to be explored.

Early studies are cautiously optimistic. In one, where older people took a prebiotic supplement for three months, measures of frailty decreased. In others, where older people received probiotic supplements, markers of inflammation were reduced. →

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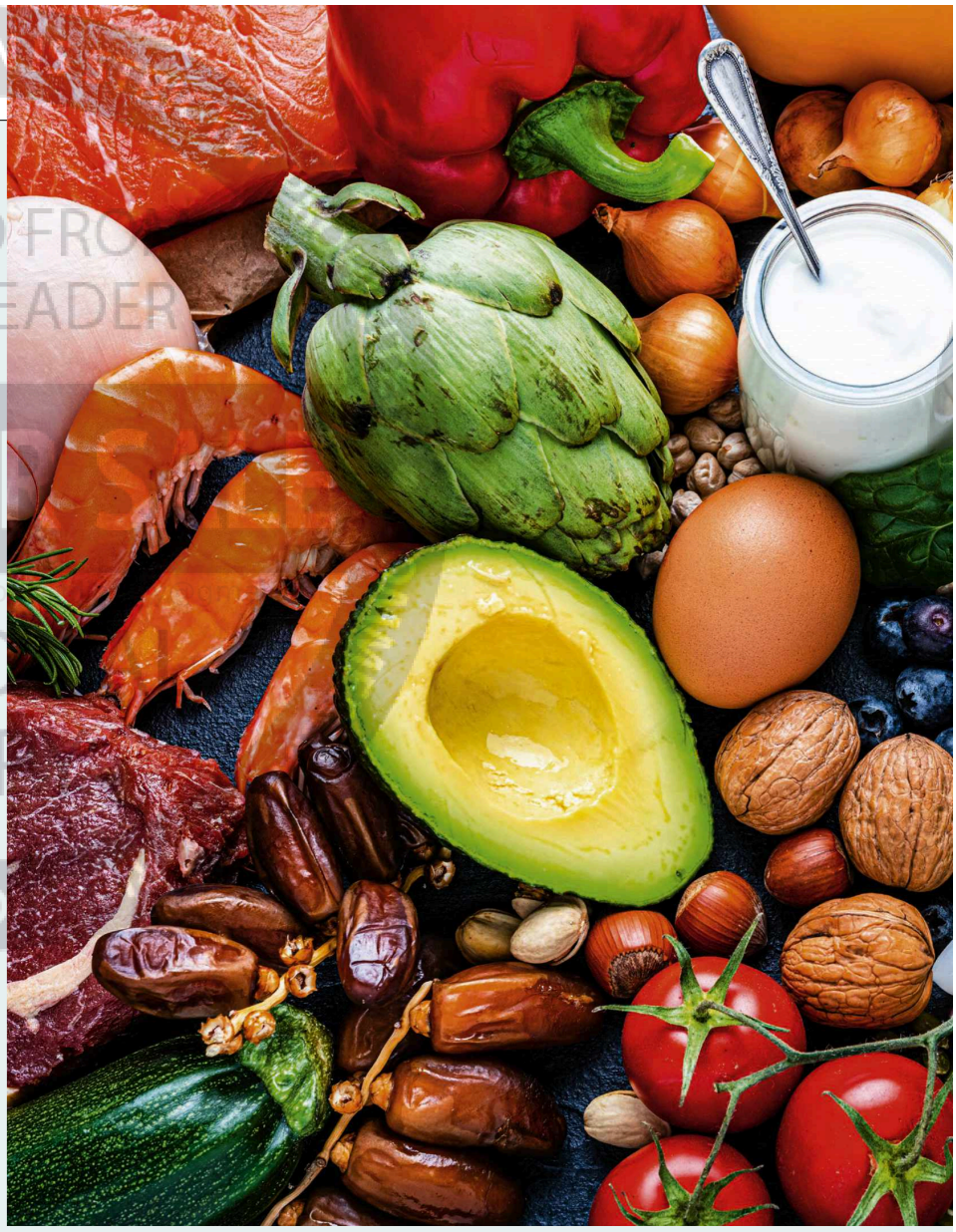


→ Research is hotting up, with animal studies hinting at further benefits. One study, from this year, found that a combined pre- and postbiotic (postbiotics are the chemicals produced by healthy gut bacteria that are thought to cause their positive effects – butyrate is one example) treatment reduced cardiac muscle damage in an animal model of heart disease.

Another study, also from this year, found that a unique cocktail of 10 probiotics eased signs and symptoms of Alzheimer's disease in a mouse model of the condition. Cognitive decline was slowed, and brain markers of the neurodegenerative condition were reduced. The study's authors called the results "remarkable."

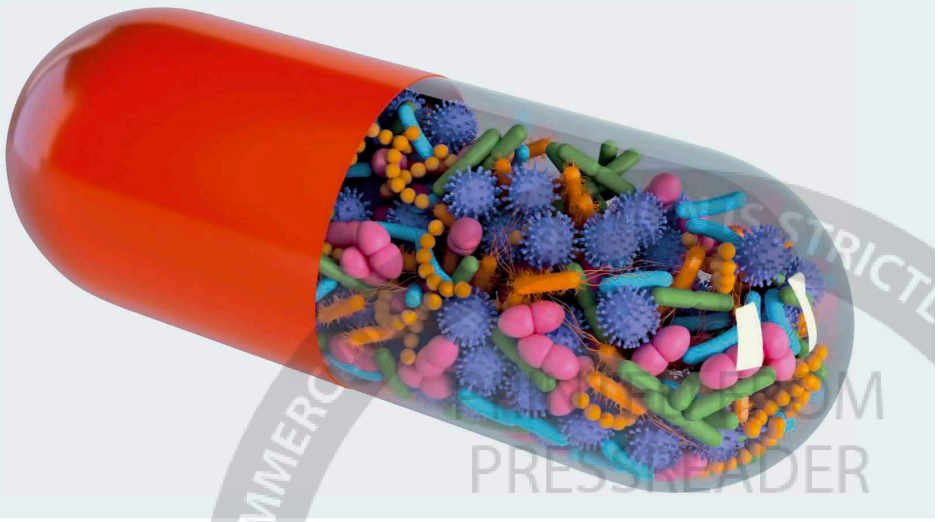
Another possible approach involves taking postbiotics. Studies suggest that Butyrate, a short-chain fatty acid, may be able to help reduce inflammation, keep the gut wall healthy and help to protect against colon cancer.

Butyrate can be bought online (it tastes awful), but researchers caution against rushing to buy it, or any of the pre- and probiotic supplements that are available. This is because, although the microbiome is highly malleable, it's almost impossible to know what blend of supplements your unique gut needs.

Microbiome tests are available, but by the time you get the results, they'll already be out of date because the microbiome is constantly changing in response to diet, activity and other factors. So, you can take a probiotic anyway, but there's no way to know if the bacteria will bed down in your gut and do something useful or pass straight through and come out the other end.

Even if your test highlights something noteworthy, such as a missing strain of 'good bacteria', it's entirely possible that you have other 'good bacteria' that already compensate for this imbalance.

"Don't waste your money," says microbiome researcher Prof Fergus Shanahan University College Cork. "One measurement doesn't mean much anyway." Instead, the single best thing that any of



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"IF YOU WANT TO PREPARE FOR OLD AGE, IT'S BEST TO START WHEN YOU'RE YOUNG"

us can do to maintain a healthy community of gut bacteria and age well, is to eat a decent diet. "I don't think we should be neurotic, trying to overcomplicate things," says Shanahan. "Just eat more fibre. Fibre is microbe food."

Study after study shows the benefits of adhering to a 'Mediterranean diet,' rich in vegetables, fruits, fish, olive oil and nuts, and low in red meat, dairy and saturated fats. Sticking to the plan is already known to improve longevity and reduce the risk of chronic diseases, such as heart disease, cancer and diabetes, but the colourful diet can help beyond this.

In the biggest study of its kind, researchers investigated what happened to the gut microbiomes of 612 healthy adults – all aged over 65 – who ate either a Mediterranean diet or their normal diet. One year on, those who had been eating Mediterranean-style had more of the gut bacteria that are linked to healthy ageing. This included more of the 'good guys' that are associated with lower frailty and better brain function, and less of the 'bad guys' that are associated with inflammation.

GETTY IMAGES X2

ABOVE Fruits, vegetables, healthy oils and fish make up a significant proportion of the Mediterranean diet

LEFT Scientists are already working to make microbial transplants via capsule a reality

The study provides the first clear evidence that eating a healthy, fibre-rich diet can help to rein in the gut bacteria known to drive unhealthy ageing and disease, but we don't need to wait until we're in our sixties to reap its benefits.

"If you want to prepare for old age, it's best to prepare when you're young," says Shanahan. "The one thing we can all do to help deterioration in old age, is to add diversity to our diet now." **SF**

by **DR HELEN PILCHER**
Helen is a science writer with a PhD in cell biology.

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