Health

How working out your ageotype could help you live healthier for longer

Your body is ageing down one of four - or more - possible pathways. Figuring out your "ageotype" could help you zero in on the things you can do to stay healthier for longer

By Graham Lawton

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THERE is a (probably apocryphal) story about Henry Ford sending agents out to junkyards across the US in search of scrapped Model Ts. The famous industrialist wanted to know which of the car's vital components failed first, so he could do something about it. The agents reported back that every bit of the car was susceptible to failure, but some were more susceptible than others, except for one – a component of the steering system called the kingpin, which almost never failed. They expected Ford to announce plans to extend the working lives of the weaker components. Instead, he ordered his engineers to make less resilient kingpins. No point wasting good money on a component that always outlived the others.

As in Model T Fords, so, too, the human body. All of our parts are susceptible to the ravages of time, but it turns out that some age more quickly than others. Exactly which parts fail first is a bit of a lottery. "Everybody's ageing differently," says Michael Snyder, a geneticist at Stanford University in California. You might have a young immune system but elderly kidneys, for example, or a decrepit metabolism but youthful liver.

Now, studies have revealed that we tend to age down one of four different pathways. This is your "ageotype" – the principle way in

which you, personally, are ageing. The bad news is that the oldest part of your body may be dragging the rest of it down. The good news is that by working out your ageotype, you might be able to target it to live healthier for longer.

The discovery of ageotypes has...

its roots in the "omics" revolution that started in the 1980s. First came genomics, the study of the genome – an organism's entire complement of DNA. Then came proteomics, the study of proteins; lipidomics, which focuses on fats; microbiomics, which deals with the bacteria, viruses and fungi that reside in and on our body; and more. When these are applied in combination and alongside standard medical diagnostics to investigate an individual's health status, it is known as "deep phenotyping", a discipline whose maxim is "the deeper you go, the more you know".

Deep phenotyping

Deep phenotyping has been used to probe the causes of all kinds of conditions, including cancer, heart disease, allergies, Parkinson's disease and addiction, to name just a handful. Until recently, however, it hadn't been applied to what is arguably the world's most serious and deadly condition: ageing.

Snyder and his colleagues decided to fill that gap. They selected 43 people aged 29 to 75 who were already enrolled in a different study. The volunteers had been deep-phenotyped at quarterly intervals over the previous two to four years. The researchers recorded data on their gene expression, metabolites, proteins, immune systems and stool and nasal microbes, while also performing a set of standard blood tests. All told, Snyder's team had access to 18,393 data points for each volunteer per quarterly test, then analysed them to see which changed significantly over the study.

This longitudinal approach – looking at the same individuals over time – is in contrast to most studies of the biology of ageing, which usually examine a group of older people and a group of younger people and note the differences between them. These studies risk comparing apples with oranges, as the older cohort may have lived in environments or had lifestyles that are no longer common in today's world, including things like indoor smoking, different diets

or more physical jobs. “Some of the stuff could be era effects as opposed to ageing effects,” says Snyder.

The new approach allowed Snyder and his colleagues to identify 608 molecules, genes and microbial species that changed significantly as the volunteers aged, even within the short window of a few years. Many were already known biomarkers of ageing, but many weren’t.

Then came the revelation. Most of the microbes, genes and molecules turned out to be associated with ageing in one of four distinct organs or systems – the kidneys, liver, immune system and general metabolism. But not everybody showed the same pattern of change. Most aged along all four trajectories at once, but with one or two predominating. “We kind of expected it,” says Snyder, “but it’s nice to see that you can measure it, and if you can measure it, you can do something about it.”

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Snyder dubbed these four broad categories ageotypes. In an immune ageotype, the immune system is biologically older than the other three. Ditto the others. It is just like the model Ts: the whole thing gets older over time, but some parts wear out quicker.

Target your ageotype

The implication is that different people will benefit from different anti-ageing strategies. “You can intervene and reverse some of these trends. We think the information is actionable through lifestyle changes,” says Snyder. He recommends metabolic agers could try to lose weight and exercise more – many studies show that a healthy weight and regular exercise can improve the processes by which the body converts food and drink into energy. Likewise, liver agers may want to quit the booze, which is related to an increased risk of liver disease. Kidney agers should drink more water – studies suggest that higher water intake is associated with a lower prevalence of chronic kidney disease and slower kidney function decline. Immune ageing is characterised by a propensity towards chronic inflammation, which underlies many conditions of

ageing, so Snyder suggests that immune agers could take turmeric or its active ingredient curcumin, which some clinical trials have shown have anti-inflammatory properties.

Happily, there are hints that some of these strategies might work. Four people in Snyder's study reversed some of their biomarkers of metabolic ageing, two by losing weight, one by taking up exercise and another by changing diet. Eight kidney agers also showed improvement, though Snyder isn't sure how. They were all prescribed statins to help lower cholesterol during the study, but the link to kidney function is unclear, he says. "I don't think they're truly reversing their ageing per se, but they're getting some [aspects] of their ageotype under control."

Lifestyle changes like quitting alcohol may slow ageing of the liver
Crystal Spires/Alamy

So how do you discover your own ageotype? Unfortunately, there is no bespoke test as yet, but Snyder says there are a few red flags to be found in standard clinical blood work. Liver and kidney function are routinely monitored, as is the level of C-reactive protein, which is an indicator of inflammation and hence immune function. Metabolic health can be roughly gauged via levels of a protein called haemoglobin A1C, which is associated with the processing of blood glucose and was routinely high in the metabolic agers in Snyder's study.

More ageotypes on the horizon

The four ageotypes are just a start. There are certainly more, says Snyder. His study was small and drawn from a limited geographical area, so is unlikely to have captured all ageotypes, says Brian Piening at the Providence Cancer Institute in Oregon, who wrote a commentary on Snyder's research.

There are already hints at what others might exist. One of the volunteers in Snyder's study appeared to have a cardiac ageotype, with a heart that was biologically older than the rest of their organs. But more examples are needed before this ageotype can be confirmed. The same applies for some other ageotypes, says Snyder. His team is now deep phenotyping a larger group of volunteers to establish more ageotypes. The researchers have

almost finished collating quarterly data over many years from more than 100 volunteers and will start analysing that data later this year.

In the meantime, other researchers claim to have extended the range of ageotypes already. Earlier this year, Kalliopi Gkouskou at the University of Athens in Greece and her colleagues reanalysed Snyder's data using different methods and unearthed five more potential ageotypes: those involving the reproductive system, sensory systems, gastrointestinal system, central nervous system and connective tissue.

Early evidence suggests that drinking more water may slow the ageing of kidney cells
JOSE CALVO/SCIENCE PHOTO LIBRARY

Likewise, in another study earlier this year, Brian Kennedy at the National University of Singapore and his colleagues applied deep phenotyping to 4066 volunteers aged between 20 and 45. They gathered information about their gut microbiome, immune system, metabolism, blood chemicals, body composition, physical fitness and facial skin, creating 403 data points for each individual.

The measurements clustered into nine ageotypes: the same four that Snyder's original study found, plus cardiovascular, physical fitness, sex hormones, facial skin features and gut microbiome. Of these, the gut microbiome was least likely to correlate with chronological age in any individual, while the liver age and sex hormone systems varied the most between individuals. This suggests that ageotypes are a real phenomenon, says Kennedy.

Meanwhile, Ye Ella Tian at the University of Melbourne, Australia, and her colleagues have dug into the impact of ageotypes on health. Earlier this year, they used data from the UK Biobank, which contains genetic, medical and lifestyle information on 50,000 middle-aged people in the UK, to develop ways to measure the biological age of seven body systems (cardiovascular, lungs, musculoskeletal, immune, kidneys, liver and metabolism) and three brain systems (grey matter, white matter and brain connectivity).

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They confirmed that different organs and systems can age at different rates within an individual and, unsurprisingly, that the oldest parts of a person's body were strongly correlated with age-related conditions they had been diagnosed with. People with renal disease had kidneys that are eight to 11 years older than their chronological age; those with diabetes had older metabolisms and people with aged cardiovascular systems were more likely to have chronic obstructive pulmonary disease (COPD). Advanced brain age was often seen in people with mild cognitive impairment, dementia and Parkinson's disease. More surprisingly, though, they found that many age-related conditions were linked to organs not typically associated with them. Advanced brain age was often seen in people with COPD and diabetes, for example.

Senescent cells

Tian's team also discovered that organs and systems don't age in isolation; they can drag others down with them. For example, a one-year increase in cardiovascular age drives a roughly 27-day increase in overall brain age. Rapidly ageing lungs lead to faster cardiovascular ageing, which in turn causes more rapid ageing of the muscles, bones and kidneys. This is perhaps due to the malign influence of senescent cells – aged, irreversibly damaged cells that don't die, but instead hang around causing bother, dripping toxins into the bloodstream and poisoning distant tissues.

But the causes of differential rates of ageing in the same body aren't yet fully understood. "There might be some genetic factors," says Tian. "Sometimes, some organ system might have a genetic predisposition that makes it more vulnerable than others. But also there are probably lifestyle factors like smoking, exercise and socioeconomic status." Snyder similarly says it may be down to a combination of genes, environment, lifestyle and medical history.

When the data is all crunched, there are likely to be dozens of ageotypes, says Snyder. "There's 78 organs [in the human body] – are there going to be 78 ageotypes? I don't think it's unreasonable to say 50 major ones." But the fact that some of these organs age in

tightly coupled ways means that this list could be whittled down to 20 or so, he says.

A new class of anti-ageing drugs has arrived – which ones really work?

A variety of drugs, including metformin, rapamycin and a host of new senolytics, are finally showing promise in clearing out zombie cells that cause age-related diseases. Here's what you need to know

All in all, the discovery of ageotypes promises to further personalise anti-ageing medicine, allowing doctors to intervene in organs and systems that are ageing fastest. And it is possible now. "Most of the clinical markers we used are available in clinical settings, so in principle those markers can be used to estimate the organ age," says Tian. "And at that stage, I think the clinician can advise some early behaviour interventions to try to delay onset of disease."

There is, however, a downside. Ageotypes cast doubt on the validity of biological age tests, says Kennedy. These generally take DNA from a very limited sample, either saliva or blood, and miss the bigger picture. "Many aspects of the human body would not be covered," he says, possibly lulling people into a false sense of security – or the opposite.

I am pretty sure I am a liver ager. I had a nasty bout of viral hepatitis when I was a teenager and haven't really looked after my liver since, regularly bombarding it with toxins, mostly ethanol. I suspect it is the most decrepit part of my 53-year-old body. But there is something I can do: eat less fat, lose a bit of weight and take an extended trip on the wagon. My liver will never be a kingpin, but I can stop it dragging the rest of me to the junkyard.

Graham Lawton is features writer at New Scientist