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Could a Mediterranean diet, rich in olive oil, fish and fresh fruit, lead to a healthy microbiome in old age?

MICROBIOME

Cultural differences

Studies of gut bacteria are beginning to untangle how diet affects health in old age — but determining cause and effect is tricky.

BY VIRGINIA HUGHES

Almost everything about eating gets more difficult with age. Elderly people typically cannot taste or smell as well as they used to, decreasing the appeal of some foods. Dental issues or a dry mouth can impede chewing; loss of muscle tone in the pharynx can make swallowing difficult; constipation and the side effects of medication can make digestion uncomfortable; and decreased mobility makes a chore of grocery shopping or cooking complex meals. Little wonder that older people eat an increasingly narrow range of foods. But can this, in itself, adversely affect health?

Recent research shows that diet influences the composition of the gut microbiome — the bacterial community in our intestines — in the elderly. In July, a group of researchers, mostly based in Ireland, published¹ the largest study so far of the microbiome in an elderly population. The data indicate that the frailest older people tend to harbour similar intestinal microbial communities. More provocatively, the study also suggests that this

microbial make-up is driven by a diet high in fat and lacking in fibre, and that a decline in our microbial community underlies ill health as we grow old.

The conclusion is controversial, as many scientists say these associations can go the other way. An individual's health, and thus the state of his or her immune system, can also affect the gut microbiota and drive eating habits.

One thing on which everyone agrees, however, is the value of finding out how to alter the microbiome in our favour. "The potential is enormous, especially the idea of figuring out what diet is right for individuals," says Rob Knight, a microbiome expert at the University of Colorado in Boulder, who was not involved in the new study. "We just don't have a very good idea yet of the specific parameters that could set the microbiota in a good direction versus a bad direction."

THOUSANDS OF HITCHHIKERS

The microbiome has received a lot of scientific attention of late. By sequencing the DNA of our microscopic stowaways, researchers have

discovered², for instance, that more than 1,000 bacterial species can live in the human gut, helping us break down food and boosting the immune system. Microbial profiles vary among individuals, with the average person harbouring about 160 different species. The intestinal microbiome is stable for most of our lives. But "at the extremes of life, both in babies and old people, it's chaotic", notes Paul O'Toole, a geneticist at University College Cork in Ireland, and leader of the new study.

There are no microorganisms in the womb; infants get their first exposure in the birth canal. Over the next few months, as babies drink milk and interact with the environment, additional species move in. The microscopic community does not settle down until about 12 months of age. But the changes that take place in the microbiome towards the end of life are less well understood.

O'Toole's interest in the subject started in 2007, when Ireland's Department of Agriculture, Food

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A nursing-home diet has a marked effect on an individual's gut microbiome.

and the Marine in Dublin started an initiative to fund research to promote the food industry. The government was particularly interested in the diets of older consumers, a group whose numbers will rise dramatically in the next couple of decades.

O'Toole received a €5-million (US\$7-million), five-year grant to study the gut microbiota of the elderly. Results from research since the 1970s suggested that he would find certain patterns. For example, several studies showed that stool samples from older people contain fewer species in the genus *Bifidobacterium* — which are thought to have beneficial health effects — than samples from middle-aged controls.

These earlier studies, however, analysed only those microorganisms that could be cultured in the laboratory, which make up about one-third of the total number of species in the gut, says O'Toole. So he set out to sequence the genes of all the organisms found in faecal samples from hundreds of people aged 65 or older, and to mine this massive data set for links between microbes and health.

CAUSE OR EFFECT?

In 2011, O'Toole's team published³ the first significant batch of data from the project, dubbed ELDERMET. Echoing previous studies, the scientists found that the diversity of species living in an individual declines with age. They also showed that the type of species lost varies greatly from person to person, meaning that the gut microbiota of two older people look more different from each other than do those

of two middle-aged people.

The latest ELDERMET study¹ aimed to find out what was driving this variability. O'Toole categorized 178 participants into four groups based on where they lived: in the general community, day hospitals, short-term hospital care or long-term nursing homes. He found that the microbial profiles of the first two groups were similar to those of 13 younger adult controls. But the profiles of the older people in institutional care were notably different: they carried a higher proportion of bacteria from the phylum Bacteroidetes, and a lower proportion from the phylum Firmicutes.

Importantly, these links correlated with diet. Residents of nursing homes often eat high-fat, low-fibre diets, heavy with starchy foods such as porridge and potatoes, fried meats, puddings and sugary juices. Outside nursing homes, older people tend to have a much more balanced diet, with more fibre, less red meat and more oily fish.

The study also found that certain microbial profiles were associated with specific health measures. For example, a gut high in Bacteroidetes correlated with several markers of inflammation, high blood pressure and small calf circumference (a measure of frailty).

The researchers also looked at the timing of these dietary and health changes. When individuals move into a nursing home, their diets change within a couple of weeks. Their microbial profiles took up to one year to change completely, whereas their health took several years to deteriorate. "The microbiota appear to be driven by what people eat," O'Toole says. And this microbial profile, in turn, "correlates with whether or not the subject is healthy or frail, inflamed or not inflamed, has lots of muscle tone or poor muscle tone."

Tracking the nursing-home residents over time adds weight to O'Toole's argument, "but there probably were other things happening to those people over the course of the year," notes James

Lewis, a specialist in epidemiology and gastroenterology at the University of Pennsylvania in Philadelphia. "We have to be cautious about trying to extrapolate too far in terms of what came first."

Lewis and several other scientists argue that there are probably many non-dietary factors influencing the microbiota of the elderly in O'Toole's study. After all, they say, some amount of weakness or frailty is generally what puts someone in a nursing home in the first place. And studies of younger adults who have acute gastroenteritis or Crohn's disease, for example, show a similar loss of microbial diversity to that seen in the elderly. "An already compromised health status could be among the major driving forces that differentiates the microbiomes of the free-living elderly from those of the long-term-care residents," says

Elena Biagi, a molecular microbiologist at the University of Bologna in Italy, who has studied the gut microbiota of centenarians.

Other factors, such as constipation and dental hygiene, could also explain part of the association. As Knight notes, when it comes to microbiome studies, "there are very few cases where cause and effect are known".

MEDITERRANEAN MODELS

There have been some short-term studies of how dietary patterns influence the microbiome. Last year, Lewis and colleagues showed⁴ that changing an individual's diet for ten days has little effect on the gut microbiome. Only long-term dietary patterns were associated with specific and stable microbial profiles.

Investigating the latter in more detail requires a more rigorous — and time-consuming — approach. That is what O'Toole and Claudio Franceschi, an immunologist at the University of Bologna, plan to use to investigate whether the so-called Mediterranean diet can help people age well.

Franceschi has been studying the elderly for more than 25 years. Several of his studies centre on the Italian island of Sardinia, which has an unusually high number of male centenarians⁵. He attributes this preponderance at least in part to the men's regular physical exercise and simple Mediterranean diet — rich in olive oil, fish, fresh vegetables and fruits. Intriguingly, this diet is also broadly similar — low in fat, high in fibre — to the diets of the healthiest elderly people in O'Toole's recent study.

Franceschi, O'Toole and two dozen other academic and industry groups are now part of a €9 million project called NU-AGE, which includes 1,250 older individuals from France, Italy, Poland, the Netherlands and the United Kingdom. For one year, half will be given the Mediterranean diet, half will remain on their normal diet, and the NU-AGE researchers will measure how their health changes. O'Toole's team will sequence the participants' gut microbiota before and after the dietary intervention, while other researchers will look at genetic, epigenetic and metabolic signatures in their blood. Each of these biological levels might give insight on how the diet changes the microbiome.

NU-AGE is exactly the kind of large, longitudinal study that scientists the world over are clamouring for. The hope is that interrogating the link between diet and the microbiome will show how some of our trillions of microbial hitchhikers can steer us to long and healthy lives — and how we can entice them to stay. ■

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