



Trust Your Gut

DO YOU HAVE THE GUTS TO KEEP YOUR BRAIN HEALTHY?

A few months into the COVID pandemic, Katharine Gorjup's life was in jeopardy from a completely different type of infection. Following a round of IV antibiotics to treat a dental infection, the Toronto woman, then 59, subsequently suffered through six months of recurrent C-difficile infections that failed to respond to one antibiotic after another.

A type of bacteria that typically doesn't cause problems in healthy individuals, C difficile can sometimes multiply out of control in the large intestine, leading to severe, potentially life-threatening diarrhea.

By the time Gorjup's doctors had exhausted the antibiotic arsenal, "I'd been living on the toilet for six months. I couldn't keep food down - I went down to 90 pounds. I looked like I was dying of cancer," Gorjup said.

What happened to Gorjup is perhaps the most obvious and dramatic example of what can happen when the community of microbes that normally live in our digestive tract - commonly known as the gut microbiome - is thrown out of balance. In Gorjup's case, antibiotics had likely decimated beneficial bowel bacteria that had previously kept C difficile in check, thereby allowing it to multiply exponentially.

Keeping the gut microbiome healthy can impact more than your body's ability to fight infection.

It can also be a key component of brain health. This article explores why this is and how to keep your gut healthy.

THE BRAIN HEALTH-GUT MICROBIOME CONNECTION

The gut microbiome is an ecosystem with a population roughly equivalent to the number of cells in our body.

It consists of a diverse mix of microorganisms, including bacteria, viruses, fungi, and bacteriophages, which carry out numerous essential functions, such as aiding digestion, synthesizing vitamins, metabolizing medications, and producing neurotransmitters similar to the brain. (Molecules that carry nerve signals throughout the body, neurotransmitters regulate mood and play key roles in cognitive functions such as learning and memory.)

The metropolis of gut microbes also affects the functioning of the immune system, and forms part of a two-way communications network between the gut and central nervous system, commonly known as the gut-brain axis.

Microbiota: The entire community of microorganisms living in or on a specific part of the body, such as the vagina, underarm, urinary tract, or colon. The most heavily populated microbiome in the human body is located in the gastrointestinal tract, and is commonly referred to as the gut microbiome.

Microbiome: This encompasses all of the microbes inhabiting a specific environment, plus their genes, and the substances they produce.

THE MICROBIOME CAN EXERT WIDE-RANGING EFFECTS THAT MAY INFLUENCE OUR SUSCEPTIBILITY TO CONDITIONS THAT AFFECT BRAIN HEALTH VIA THE GUT-BRAIN AXIS.

Dr. Siobhain O'Mahony, a principal investigator and senior lecturer at APC Microbiome Ireland, University College Cork, Ireland, explained how these systems interact. "The products the microbiota produce can directly and indirectly affect the peripheral nervous system as well as the central nervous system."

She continued, "They can also influence the brain via the vagus nerve, which connects the bowel to the brain. As well, they can produce cytokines that are anti-inflammatory or pro-inflammatory, to impact the immune system directly."

SEX DIFFERENCES IN THE GUT MICROBIOME

Sex hormones seem to affect the makeup of the gut microbiome, and conversely, the gut microbiota can influence levels of these hormones in the blood. Generally speaking, before menopause, women appear to have greater diversity in their gut microbiota than men, and the composition differs, too, with the abundance of certain bacteria differing between the sexes.

"There are actually receptors for gonadal hormones - so estrogen, progesterone and testosterone - on bacteria," in the gut, Dr. O'Mahony said. "So that gives us an idea that there's an interaction between them".

As well, "there are huge changes in the gut microbiome during pregnancy, puberty, and menopause." There is also some evidence that the gut microbiome in women and men can respond differently to an identical intervention.

In people with obesity, and post-menopausal women, differences between the sexes shrink substantially. →

THE GUT MICROBIOME COMPOSITION MAY ALSO PLAY A MORE SIGNIFICANT ROLE IN OBESITY FOR WOMEN THAN MEN.

It could potentially contribute to increased blood pressure – linked with a higher risk of developing cognitive impairment and dementia – particularly before menopause.

However, more research is needed to unravel the complex interactions between sex hormones, the gut microbiota, and the immune system and how they might influence women's brain health.

THE LEAKY GUT EFFECT

Differences in the composition and function of the microbiome have been linked to a host of diseases, including such neurological disorders as Alzheimer's disease (AD), as well as conditions that are associated with an increased risk of cognitive decline and dementia, including cardiovascular disease, Type 2 diabetes, and frailty.

Ongoing low-grade immune system overactivity appears to be a common contributor to these problems. One thing that can lead to this misplaced immune activation is the gut lining changing from its normal tightly sealed structure to a barrier that's easier for microbiota to get through.

Roughly 70% of the immune cells in the body can be found in the intestines.

These immune cells are primarily situated behind a delicate barrier of closely joined cells known as the epithelium. This barrier is usually coated with a dense layer of mucus that acts as a shield, preventing the microbiota from entering.

When this double-layered defensive line becomes impaired in some way, "parts of bacteria, or bacteria themselves, can leak out into the systemic blood system," Dr. O'Mahony said, which in turn "creates an immune response."

Research by Dr. O'Mahony and others has established that stress hormones, such as cortisol, "can increase bowel permeability and can change the gut microbiome," she said.



DURING PREGNANCY, WHEN THERE IS STRESS, ANXIETY, AND DEPRESSION, EVEN AT SUBCLINICAL LEVELS, WE'VE FOUND CHANGES TO CIRCULATING FACTORS IN THE MOTHER'S BLOOD THAT INDICATE HER BOWEL IS MORE PERMEABLE.

According to an April 2022 review article published in the journal *Frontiers in Nutrition*, "the leakage of the intestinal barrier and

the disruption of the gut microbiome are increasingly recognized as key factors in different pathophysiological conditions," including cardiovascular diseases, obesity, and Type 2 diabetes.

Similarly, these factors may play a role in the progression of AD. According to a review published in the *Journal of Neurogastroenterology and Motility* in January 2019, "alterations in the gut microbiota composition induce increased permeability of the gut barrier and immune activation, leading to systemic inflammation, which may, in turn, impair the blood-brain barrier and promote neuroinflammation, neural injury, and ultimately neurodegeneration."

HOW GUT HEALTH IMPACTS FRAILITY

There also appears to be links between the richness of diversity in the gut microbiome and susceptibility to age-related conditions, like frailty, that are risk factors for cognitive impairment and inflammation.

"It is very clear that people living in care homes generally tend to have less diverse microbiomes" and higher levels of frailty "than older people living in the community," said Dr. Emma Allen-Vercoe, professor and Canada Research Chair in the Department of Molecular and Cellular Biology at the University of Guelph.

And some research, such as a study that used data from 143,215 participants in the UK Biobank, has shown that, "individuals with pre-frailty and frailty were at a higher risk of dementia incidence even after adjusting for a wide range of confounding factors." This article was published in *The Lancet: Healthy Longevity* in November 2020.

Other evidence points to a connection between higher levels of inflammation and frailty. Take, for example, the research results published in *Frontiers in Psychology*. In the 2022 systematic review, which spanned 22 studies (comprising a total of 17,373 mostly community-dwelling participants), 95% showed significant links between inflammation (and in particular, high levels of inflammatory markers C-reactive protein and interleukin-6) and frailty status.

Admittedly, due to the observational nature of studies such as those examining the relationship between gut microbiome composition and frailty, "it's hard to know whether the situation the individuals are living in led to the lack of diversity, or the lack of diversity led to frailty," noted Dr. Allen-Vercoe.

"But we do have a few clues. Some of those are the wealth of data we now have that shows exposures to medicines, such as antibiotics, poor foods, and living an isolated lifestyle tends to reduce the diversity of your microbes," she added.

CAN YOU BOOST YOUR GUT MICROBIOME?

With all the research that's been done to date, "we don't know what a healthy microbiome looks like," said Dr. Natasha Haskey, a registered dietician and post-doctoral fellow in the Irving K. Barber Faculty of Science's Department of Biology at the University of British Columbia's Okanagan campus in Kelowna.

"You and I might both be healthy, healthy being the absence of disease, but our microbiome fingerprints might be quite different," she said. Consequently, it's impossible to predict the effect of a specific intervention to manipulate the microbiome on a given individual.

SOME LIFESTYLE MEASURES, THOUGH, PROMOTE INCREASED DIVERSITY IN THE GUT MICROBIOME WHILE DAMPENING DAMAGING INFLAMMATION.

"One way we can change the microbiome is through what we eat," Dr. Haskey said. "If people start consuming a healthier diet, we can see changes in the microbiome within a week, which stay relatively stable as long as they stay on the particular diet." In fact, according to Dr. Haskey, diet and antibiotic use are the two modifiable factors with the strongest influence on gut microbiome health.

The eating pattern Dr. Haskey recommends is a Mediterranean-style diet since, according to existing research, it helps achieve what she called "a sort of balanced inflammation. I personally don't like the word anti-inflammatory since we do need some inflammation in our body to stay healthy."

"It doesn't have to be vegetarian or vegan, but it is plant-forward," she said.



You can eat a variety of healthy foods, but one of the key components is colourful fruits and vegetables, rich in polyphenols.

These compounds promote a healthy balance of gut microbiota. Vegetables, fruits, and other plant foods such as beans, legumes, and whole grains, are also abundant in dietary fibre.

Dietary fibre is broken down by certain species of gut microbiota through fermentation, to produce short chain fatty acids (SCFAs), which, among many other functions, play important roles in regulating immune function and protecting the integrity of the intestinal barrier.

Rather than emphasizing low fat intake, the Mediterranean diet is "rich in monounsaturated fats," Dr. Haskey explained, found in such foods as olive oil, avocado, nuts, and seeds. Fish and seafood, which are sources of omega-3 fats, are recommended, too.

Dr. Haskey's dietary prescription "also includes dairy products," she said. "In some of my work, we've seen that milk fat has a protective effect on the intestinal barrier. We've found a metabolic benefit to dairy. It's not one fat on its own, it's a blend of fats unique about the Mediterranean diet."

At the same time, Dr. Haskey recommends limiting omega-6 fats from such oils as corn, safflower, and sunflower, all of which may hide on the labels of ultra-processed foods under the term "vegetable oil." She noted, "In our mechanistic studies, we saw [omega-6s] had a detrimental effect on inflammation."

ANOTHER REASON TO CURB CONSUMPTION OF ULTRA-PROCESSED FOODS IS TO MINIMIZE INTAKE OF SUCH ADDITIVES AS ARTIFICIAL SWEETENERS AND EMULSIFIERS, WHICH ARE USED TO IMPROVE TEXTURE AND EXTEND SHELF LIFE.

"We're just beginning to understand their impact on the microbiome," Dr. Haskey said, but there are indications some may be potentially harmful. She cited the example of research that has shown certain emulsifiers influence the mucus that lines the digestive tract, creating more of a thin layer.

It also may be worth increasing the intake of foods not always mentioned in the same breath as the Mediterranean diet. "There have been a few papers lately which showed benefits of fermented foods over and above just a high-fibre diet," noted Dr. Jeremy Burton, —→

Probiotics: According to the International Scientific Association for Probiotics and Prebiotics (ISAPP), these are "live organisms that, when administered in adequate amounts, confer a health benefit on the host." Strictly speaking, this includes only strains with scientifically documented effects. The live microbes in traditional fermented foods and beverages such as kimchi, sauerkraut, and kefir, "typically do not meet the required evidence level" to qualify as probiotics. For a list of probiotic products that have been shown to be effective for treating specific conditions, visit probioticchart.ca

Prebiotics: These are substances that we can't digest, but which serve as food for microbes in our gut that perform beneficial functions. This includes many, but not all, types of dietary fibre, one being inulin, which is found in such plant foods as chicory root and onions.

who holds the Chair of Human Microbiome and Probiotics at the Lawson Health Research Institute and St. Joseph's Health Care London, and is an associate professor at Western University's Schulich School of Medicine and Dentistry in London, Ont.

For example, in one study published online in August 2021 in *Cell*, 36 healthy adults were randomly assigned to increase their intake of either high-fibre or fermented foods, such as yogurt, kefir, cottage cheese, kombucha, fermented vegetables such as kimchi, and vegetable brine drinks.

After ten weeks, those in the fermented food group saw an increase in gut microbiota diversity and a drop in levels of 19 inflammatory proteins, including one associated with such conditions as Type 2 diabetes.

It's not yet clear whether it is the microorganisms responsible for fermentation, or compounds in the fermented foods, that bring about these beneficial changes

Perhaps the greatest medical advance to come out of gut microbiome research to date is treating recurrent C-difficile infection by re-seeding the patient's bowel with a sample population of microbiota. This is typically done by directly

introducing stool from a healthy donor (fecal transplant) by enema or oral capsules.

The approach has become standard at such centres as St. Joseph's Health Care London, where Katharine Gorjup received this treatment, seeing her condition return to near normal within days.

Research like this should lead to much less crude, more targeted therapies for preventing diseases like dementia. For example, Dr. Allen-Vercoe predicts that irritable bowel syndrome, which is linked with heightened dementia risk, will one day be managed with ongoing supplementation to replace the microbial metabolites missing in people with the disease.

In the meantime, however, the strategy with the most evidence behind it is paying closer attention to what you put on your plate. As Dr. Burton put it, "what you eat is what you are with regards to your microbiome." 🍌

