# Study links gut microbiome changes to increased risk of type 2 diabetes

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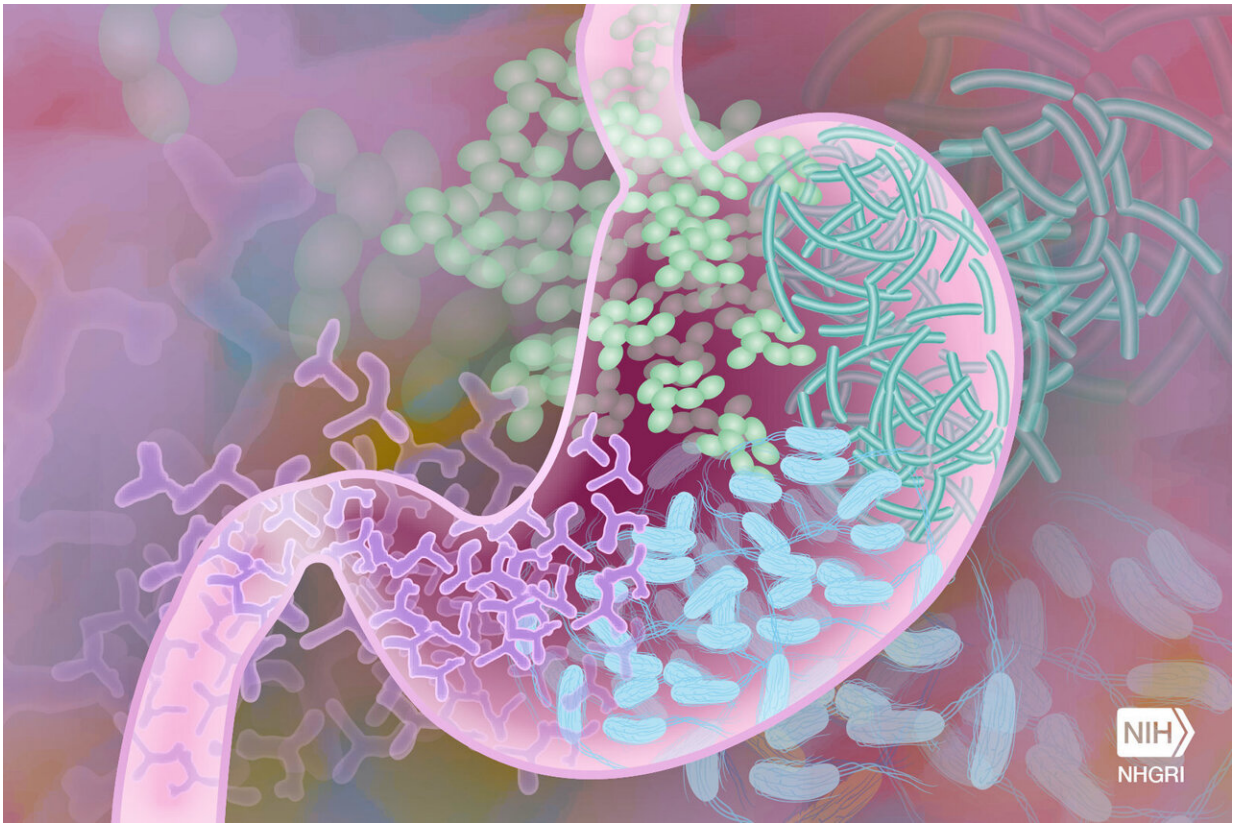


Illustration of bacteria in the human gut. Credit: Darryl Leja, National Human Genome Research Institute, National Institutes of Health

The largest and most ethnically and geographically comprehensive investigation to date of the gut microbiome of people with type 2

diabetes (T2D), prediabetes, and healthy glucose status has found that specific viruses and genetic variants within bacteria correspond with changes in gut microbiome function and T2D risk.

Results of the study—which represents a collaboration across Brigham and Women's Hospital, the Broad Institute of MIT and Harvard, and Harvard T.H. Chan School of Public Health—are published in *Nature Medicine*.

"The microbiome is highly variable across different geographic locations and racial and ethnic groups. If you only study a small, homogeneous population, you will probably miss something," said co-corresponding author Daniel (Dong) Wang, MD, ScD, of the Channing Division of Network Medicine at Brigham and Women's Hospital, Broad, and Harvard Chan School. "Our study is by far the largest and most diverse study of its kind."

"The gut microbiome's relationship to complex, chronic, heterogeneous diseases like T2D is quite subtle," said co-corresponding author Curtis Huttenhower, Ph.D. of Harvard Chan School and Broad. "Much like studies of large human populations have been crucial for understanding human genetic variation, large and diverse populations are necessary—and increasingly feasible—for detailed microbiome variation studies as well."

T2D affects approximately 537 million people worldwide. In T2D, the body gradually loses its ability to regulate blood sugar effectively. Research over the last decade has linked changes in the gut microbiome—the collection of bacteria, fungi, and viruses that inhabit our intestines—to the development of T2D. However, prior studies of the gut microbiome and its role in T2D have been too small and varied in study design to draw significant conclusions.

This paper analyzed data from the newly established Microbiome and Cardiometabolic Disease Consortium (MicroCardio). The investigation included newly generated data and those originally captured during several other experiments, encompassing a total of 8,117 gut microbiome metagenomes from ethnically and geographically diverse participants.

People included in the study had T2D, prediabetes, or no changes in their blood sugar levels and hailed from the U.S., Israel, Sweden, Finland, Denmark, Germany, France, and China. Co-first authors on the paper are Zhendong Mei, Ph.D., of the Channing Division of Network Medicine at Brigham and Women's Hospital and Broad, as well as Fenglei Wang, Ph.D., of Harvard Chan School and Broad.

"With this large study, we asked two questions. One is, 'What are the roles of species and strains that make up the gut microbiome in type 2 diabetes?' The other question is, 'What are these microbes doing?'" Wang said. "When we analyzed this data, we found a relatively consistent set of microbial species linked to type 2 diabetes across our study populations. Many of those species have never been reported before."

To understand the role of these microbes in the gut, the team analyzed species' functional abilities. Different strains of a microbial species can have varied functions, like the ability to make a specific amino acid. The team found that certain strains had functions that may be linked to varied T2D disease risk.

One major functional difference they saw was that a strain of Prevotella copri—a common microbe in the gut that has the capacity to produce large amounts of branched-chain amino acids (BCAAs)—was more commonly seen in diabetes patients' gut microbiomes. Previous studies have shown that people with chronically high blood levels of BCAAs

have a higher risk of obesity and T2D.

The researchers also found evidence suggesting that bacteriophages—viruses that infect bacteria—could be driving some of the changes they detected within certain strains of gut bacteria.

"Our findings related to bacteriophages were very surprising," Wang said. "This could mean that the virus infects the bacteria and changes its function in a way that increases or decreases type 2 diabetes risk, but more work is needed to understand this connection."

In another analysis, the team studied a small subset of samples from patients newly diagnosed with T2D to assess microbiomes that are less likely to have been impacted by medication use or long-term high glucose status. Their results were similar to their larger findings, according to Wang.

"We believe that changes in the gut microbiome cause type 2 diabetes," said Wang. "The changes to the microbiome may happen first, and diabetes develops later, not the other way around—although future prospective or interventional studies are needed to prove this relation firmly."

"If these microbial features are causal, we can find a way to change the microbiome and reduce type 2 diabetes risk," he added. "The microbiome is amenable to intervention—meaning you can change your microbiome, for example, with dietary changes, probiotics, or fecal transplants."

One major limitation of the study is that, for the most part, it looked at patients' microbiomes at one point in time. It didn't look at changes to the gut microbiome or disease status over time. Future studies that build on this work include studying this link over an extended period and

examining the strain-specific functions to understand better how they lead to T2D.

"A benefit and a challenge of the human microbiome is that it is highly personalized," said Huttenhower. "The fact that we each have highly distinct microbial communities and microbial genetics means that very large population studies are needed to find consistent patterns. But once we do, individual microbiomes have the potential to be reshaped to help reduce disease risk."

**More information:** Mei, Z et al. Strain-Specific gut microbial signatures in Type 2 Diabetes Revealed by a Cross-Cohort Analysis of 8,117 Metagenomes, *Nature Medicine* (2024). DOI: 10.1038/s41591-024-03067-7

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