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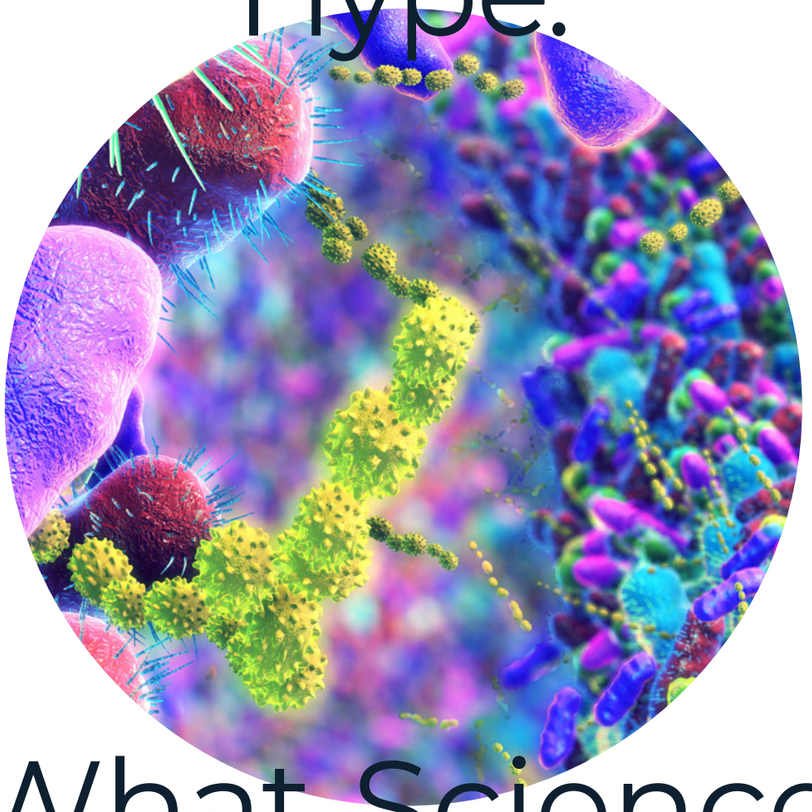

What Science Really Says About Your Gut Bacteria

MICROBIOME

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The gut microbiome has become a scientific and public fascination, with new studies and health claims emerging daily. While diet is often cited as the key factor shaping gut bacteria, research suggests a far more complex picture. With over 200 variables influencing an individual's microbiome and only a fraction of its variability explained, the idea of a universally "healthy" gut remains elusive. Popular microbiome tests and interventions may not tell the whole story – especially when stool samples only offer a partial snapshot of the vast intestinal ecosystem. This article explores the intricate relationship between diet, microbiome diversity, and health, challenging common assumptions and highlighting the unanswered questions in this rapidly evolving field.

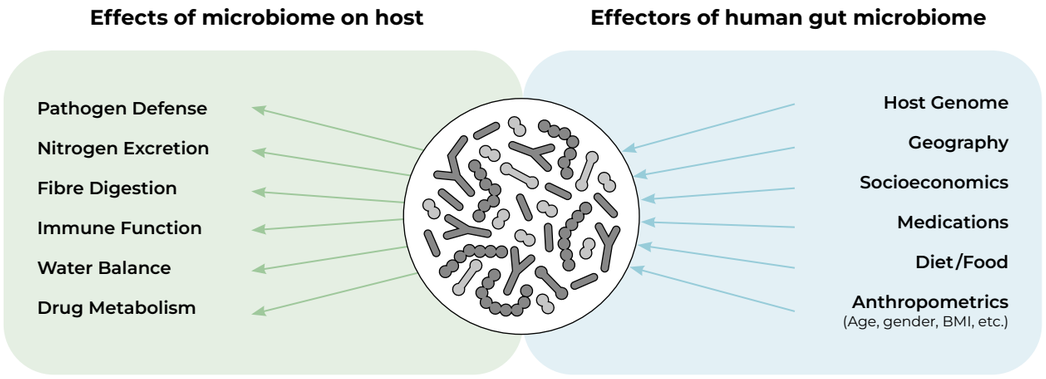
Recent years have generated an enormous interest in the gut microbiome in both the academic arena but also in the public domain. Dozens of new scientific papers appear on a daily basis, and the media are eager to immediately bring new findings to the public. This has caused a growing demand for products and services – with many companies offering microbiome profiling from a self-collected stool sample, usually coupled to advice on "how to shape the microbiome", or by offering prebiotics, probiotics or symbiotics. And it is generally believed and often stated that nutrition is the most important factor in defining and altering the gut microbiome. However, numerous studies have now identified around 200 variables that contribute to an individual's microbiome, and which, in total, can currently explain around 15–20% of the variance found in a population. That leaves most of the variability in the human gut microbiome so far unexplained (1). This also calls for caution in using the term dysbiosis, which suggests an altered or "unhealthy" state of the microbiome. What characterises a "healthy" microbiome is essentially not known and subject to scientific discussion (2); although most experts seem to agree that a high species diversity is the expression of a healthy microbiome (3). A high diversity is often found in populations that live in rural environments, and their microbiome often matches that of prehistoric humans, but they also quite often carry nematodes in their gut (4,5), and these seem to drive bacterial diversity and are thus a major confounder in the diversity debate. What should always be kept in mind is that the microbiome as determined in a stool sample does not truly represent the ecosystem found in the large intestine which hosts the majority of bacteria (6) and, moreover, almost all studies found have relative abundance of bacteria as outcome. But this does not match with the true number of bacteria (7) and, when bacterial numbers rather than relative abundance are taken as outcome measure, some of the associations of gut microbiome profiles with diseases (from diabetes to Alzheimer dementia and many others) are less strong or even vanish (8). What also needs to be considered is that stool volume and frequency, stool water content and stool appearance (colour and consistency) are critical determinants of bacterial density and diversity in a faecal sample (9,10). Those parameters are also quite different in people living in rural, low-income as compared to high-income countries (11) and that may as well define the differences in bacterial diversity. However, these large differences in microbiomes are often interpreted as a consequence of "unhealthy diets" consumed in high income countries that then promote non-communicable diseases.

Exposure of the host to a large spectrum of bacteria and their products constantly challenges the host immune system, of which a large part is found in the intestine, with a high density of immune cells in the lamina propria (see Fig. 1).

FIGURE 1

The Gut Microbiome – Facts and Figures

Colonic volume:	~ 100–250 ml
Microbiome mass:	~ 100–150 g
Bacterial density:	~ 10^4/g in small intestine ~ 10^7/g in colon
Number of species:	3.000 different identified individuals harbor ~ 200–400 species



The diversity of the microbiome is thus a critical factor in immune system conditioning and its ability to generate immune tolerance towards millions of harmless microorganisms in the lumen, and to summon rapid responses to fight pathogenic bacteria. Although the intestinal lining is covered with a mucus layer that is comprised of a sticky inner and almost sterile part adjacent to the epithelium and a fluffy outer layer in which bacteria can be found at low density, the underlying immune system receives a multitude of signals from the lumen to adapt accordingly.

Diets and gut microbiome – energetics effects

The gut microbiome is estimated to represent 50-100 g of bacterial mass (12), with the highest density of bacteria in colon. Around 15g of bacteria are excreted in faeces per day and need to be replaced (13). That requires 100 to 200 kcal* per day for bacterial growth and maintenance of this biomass. During extended fasting/starvation, the microbiome changes substantially (14). In the absence of food intake, bacteria live on nutrients that enter the gut from secretions and from the glycoproteins of the gastrointestinal mucus and shaded mucosal cells.

Diet has a direct effect on the microbiome and delivers "food" for the bacteria – mainly in the form of otherwise non-digestible and usable dietary fibres from cell walls or storage carbohydrates such as inulin and other sugars in plant-based diets. These are substrates for bacterial metabolism and deliver a variety of short-chain organic acids, of which the short-chain fatty acids (SCFA) – mainly acetate, butyrate and propionate – are the dominant types. They are partially absorbed and provide the host with 1.5 to 2.0 kcal/g. Butyrate is mainly used by the colonic tissue as an energy substrate, while propionate and acetate are mainly utilised in the liver.

Around 200 variables contribute to an individual's microbiome.

It is interesting to observe that very few of the thousands of scientific papers on the human gut microbiome have examined how much energy is excreted with the stool. With the idea that the gut microbiome contributes to overweight and obesity, the amount of calories excreted from the amount of energy ingested through food and drink becomes an issue. Careful analysis of energy excretion with a dye technique revealed that around 8% of the calories ingested are found in the stool (15,16). In order to calculate how many calories are made available to the host from the utilisation of undigested food components in the colon, the amount of calories that pass from the small into the large intestine needs to be known. This is of course not easy to determine and can only be estimated from studies in patients with an ileostomy, which allows the collection of gut contents that would normally pass into the colon. These studies show that an estimated 300 kcal per day are released to the microorganisms in the colon, of which around 200 kcal are then found in faeces, leaving around 100 to 150 kcal that can be obtained by the host from microbial metabolism. It is hard to imagine that differences in this small amount between individuals has a major influence on the development of the host's body weight. Moreover, various trials, in which faeces from lean or obese individuals were transplanted into the intestines of lean or obese volunteers to investigate the effects on body weight, did not observe any significant effects on body weight management. A recent thorough re-analysis of all rodent studies that originally suggested that the microbiome was a significant contributor to obesity in mice and rats also concluded that the influence of the microbiome, if at all, is very small (17).

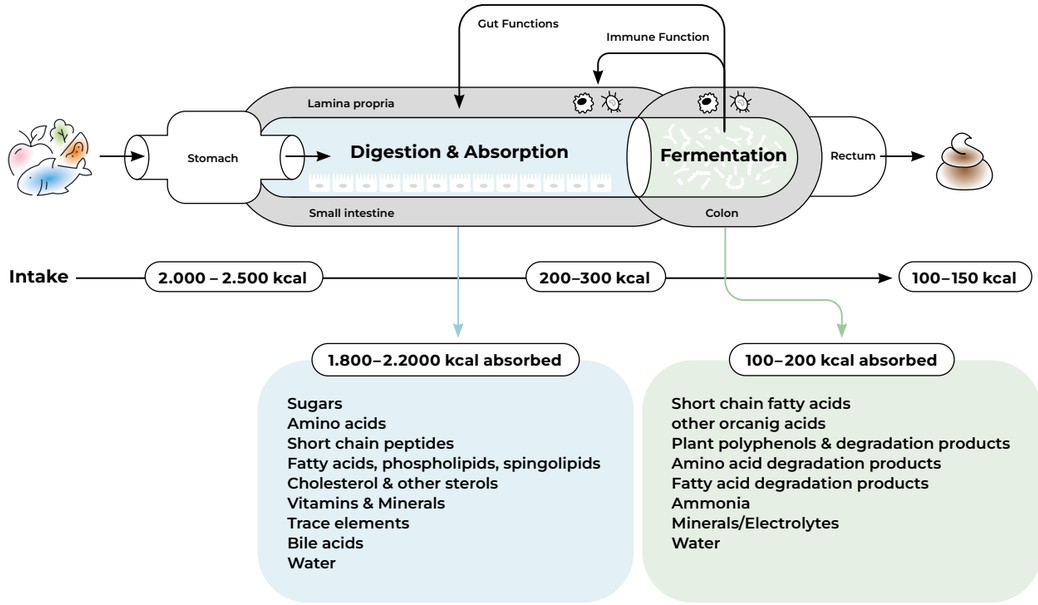
Diets and microbiome – qualitative aspects

With reference to the diversity of the gut microbiome as a surrogate for a "healthy microbiome", very recent studies have compared the diversity in faecal samples from vegans, vegetarians and omnivores. A study of > 21,000 individuals from 5 international cohorts found only minor differences in bacterial richness, with significant differences in only two cohorts, where richness was greater in omnivores than in vegans (18). From a similar study but with only around 30 individuals in each arm, the authors conclude: "compared to the general inter-individual differences, habitual diet appears to have a limited effect on the composition of the microbiota at the species level" (19). An early study in which volunteers ate a vegan diet for 5 days, and after a five-day washout period ate only animal products (20), also found only minor differences in the measurement of bacterial diversity, despite major differences in nutrient and fibre intake. When a Mediterranean diet with 54 g of fibre was tested on healthy volunteers compared to a Western-style diet with only 5g of fibre per day, the differences in bacterial diversity were also minor, and the authors stated: "taxonomic profiles of microbial communities in faecal samples were similar, suggesting little influence of the diet on the core members of the gut microbiota" (21). Intervention studies with fermentable fibres consistently found a selective increase in Bifidobacteria species and SCFA, while microbial diversity remained unaltered against a background of high inter-individual variability (22,23).

Gut bacteria and their diverse biochemical capacities can produce a huge spectrum of metabolites that, when absorbed, can affect host metabolism.

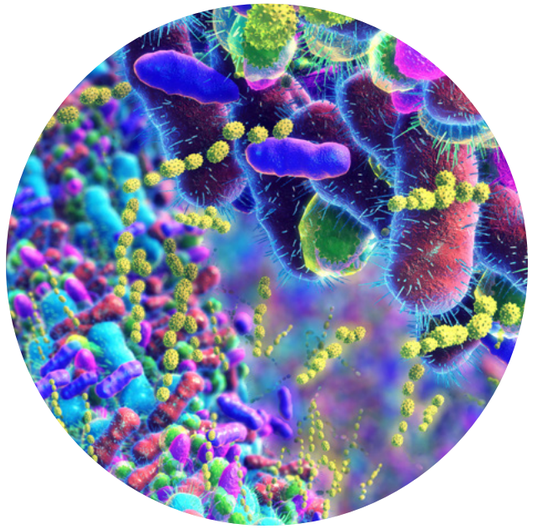
FIGURE 2

Digestion, Absorption and Fermentation



Many of the hundreds of plant constituents that we consume with fruits and vegetables enter the colon and are transformed into hundreds of different chemicals (24). They partially appear in the blood and are later excreted via urine. The spectrum of these compounds can vary greatly from person to person, and their biological activities are correspondingly quite different. Products of bacterial transformation of ingested diet components are often modified further in the human metabolism and some of those products are considered to contribute to the development of chronic diseases, examples are TMAO (trimethylamine oxide) or PAG (phenylacetylglutamine), which are both considered to participate in the development of cardiovascular diseases (25). But the repertoire of compounds produced by the gut microbiome that influence human health for “better or for worse” is still emerging.

All in all, research in recent years has produced a wealth of information about the gut microbiome. This development has been driven primarily by low-cost, high-throughput sequencing, data processing and interpretation techniques. The presence of microbes in the human large intestine and their ability to produce the beneficial SCFA has been known for decades, but modern life sciences essentially ignored their role in health and disease. This has changed drastically – new findings about the microbiome appear in the public domain every day, suggesting even to non-experts that it is of the utmost importance for health and disease, and that changes in the composition of the microbiome in turn have a major impact. It is obvious that our diet has an influence on the microbiome and the associated health impacts. However, thorough studies suggest that the effects are minimal, at least in terms of microbiome diversity, which is considered an indicator of a healthy microbiome. The biological activities of the bacteria are diverse and the substances they produce are extremely varied. Their functions are not yet fully understood. The greatest challenge facing any approach to intervention – whether through diet, medication or dietary supplements – is the enormous and largely unexplained variability in the microbial spectrum between individuals.



Glossary

Microbiome and Microbiota
Microbiota describes the living microorganisms found in a defined environment. Microbiome refers to the collection of genomes from all the microorganisms in the environment, which includes not only the community of the microorganisms, but also the microbial structural elements, metabolites, and the environmental conditions (taken from Hou, K., Wu, ZX., Chen, XY. et al. Microbiota in health and diseases. Sig Transduct Target Ther 7, 135 (2022). https://doi.org/10.1038/s41392-022-00974-4).

Probiotics
Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host according to the definition of the International Association of Probiotics and Prebiotics 2016.

Prebiotics
A substrate that is selectively utilized by host microorganisms conferring a health benefit according to the definition of the International Association of Probiotics and Prebiotics 2016.

Symbiotics
A combination of probiotics and prebiotics.

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