Yakult
Science for Health

# EXPLORING THE LATEST RESEARCH INTO DIETARY INFLUENCES ON THE GUT MICROBIOME

YAKULT STUDY DAY
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## INTRODUCTION FROM DR LOUISE DURRANT RD, SCIENCE MANAGER, YAKULT

I was delighted to chair the first Yakult Study Day of 2021 and invite four eminent speakers to explore the latest research into dietary influences on the gut microbiome. With the internet improving consumers' access to a greater range of scientific information, there is more need than ever for healthcare professionals to keep up to date with the science. This can be challenging to fit into our busy lives which is why Yakult continues to provide opportunities, through its study days, science summaries and dedicated website, for healthcare professionals to access expert knowledge about gut health and the role of probiotics and other modulators of the gut microbiome.

## SUPPORTING CONSUMER INTEREST IN THE GUT MICROBIOME – OPPORTUNITIES AND CHALLENGES

Health professionals are ideally placed to provide advice about diet and gut health as they are a trusted source of health information. But many would welcome support to keep up with new research and resources to help them deliver accurate dietary advice when patient contact time with is limited. That was the key message from the presentation by Sara Stanner, British Nutrition Foundation (BNF), who went on to discuss:

- **Trends driving consumer interest in gut health;**
- **Where consumers and healthcare professionals get their information around diet and the microbiome;**
- **The challenges for healthcare professionals in keeping up to date with the latest evidence; and**
- **Ways in which healthcare professionals can capitalise on consumer interest in gut health to promote healthier dietary habits.**

## CONSUMER TRENDS

In recent years the microbiome, the trillions of microorganisms like bacteria, viruses and fungi in our gut, has attracted a huge amount of attention in the scientific community and it has become clear that they provide metabolic, immunologic and other functions that play a crucial role in human health. Media coverage of new findings has stimulated the general public's interest in the role of the gut microbiota in weight management, cardiovascular health, metabolic control, cancer and even mood!

During the coronavirus pandemic, gut health has become more relevant as research links Covid-19 disease severity to gut dysbiosis – defined as 'any change to the composition of resident commensal communities relative to the community found in healthy individuals'[1]. Observational studies showed patients with Covid-19 to have a different gut microbiota composition, particularly depleted in immune-supporting species such as *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii*, compared with non-Covid-19 patients[2]. Lower numbers of these species were also associated with more severe disease and the microbiota differences persisted even after patients recover from Covid-19, leading some commentators to suggest that this could explain why some patients go on to develop so-called 'long Covid-19'.

## PERSONALISATION

It has been suggested that the gut microbiome may be a factor in determining our response to different nutrients, foods and diets. A startling fact is that humans are around 99.9% identical to one another in terms of their genome but our gut microbiome can differ by 80-90%[3]. This makes us all truly unique. Studies, like the American & British Gut Project[4] – which invites citizens to submit faecal samples for analysis – are trying to create a databank of the myriad of species that thrive in our guts and link these with health and lifestyle. Some studies have shown the microbiome to affect the metabolic response to fibre in bread[5], or to calorie restriction[6] as well as how patients with irritable bowel syndrome respond to a low FODMAP diet[7]. But it's still too early to draw conclusions about whether our microbiome can help predict what type of diet might be best for any one of us.

What we eat impacts on our microbiota – and there are opportunities for intervention since the microbiota isn't static and responds relatively quickly to dietary change. In one fascinating study, 350 hunter gatherers in Tanzania provided stool samples over a year[8]. The results revealed that their gut microbiota cycled markedly between the wet and dry seasons when diets were based mainly on plant versus animal foods respectively.

### TERMINOLOGY

**Gut microbiota** – the community of microorganisms living in the human gut.

**Microbiome** – the microbiota and their genes.

**Gut dysbiosis** – an imbalance of gut microbiota species relative to the norm, which increases the risk of ill-health.

**Pathogen** – microorganisms with the potential to cause disease.

**Probiotic** – live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host.

**Prebiotic** – a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health.

## IMPORTANCE OF FIBRE

Dietary fibre is one of the most important aspects of diet when it comes to influencing the gut microbiota – and it also appears to be a clear driver of health outcomes, such as risk of type 2 diabetes, colorectal cancer and cardiovascular disease. Despite this, intakes of fibre remain stubbornly low. Moving the average UK consumer, who has a daily fibre intake of 19g[9], to the recommended 30g will take a colossal effort as current diets simply don't contain enough high fibre foods such as wholegrains, nuts, seeds, beans, pulses, fruits and vegetables to achieve this level of intake.

Part of the problem is consumer perception. According to a survey carried out by the IGD, many consumers think high fibre foods are 'brown', expensive, tasteless and take a lot of effort to cook[10]. Another aspect is knowledge as many don't know where to find fibre or how much they should be eating. The lack of visibility of fibre on front-of-pack food labels may be also contribute to it being less 'front of mind' compared to fat, sugar or salt.

## WHERE DO PROBIOTICS FIT IN?

Interest in probiotics is on the rise and reflected in the massive increase in the global demand. Yet, most people appear to get their information from advertisements, family, friends and the internet, rather than from healthcare professionals[11]. This creates challenges as probiotic efficacy depends on several factors including clinical need, bacterial strain, and adherence to dose, frequency of consumption and duration. Tailored advice is therefore important.

Healthcare professionals are best placed to advise but some seem to be sceptical about the benefits, especially when unfamiliar with the literature[11]. This could be improved by more guidance from bodies such as NICE, and easy to access resources summarising their benefits for different conditions. For example, an online hub with independent assessment of probiotic studies, as provided in Canada[12] might be helpful.

Consumer interest in gut health also embraces fermented foods, such as kimchi, kefir and kombucha. Research on these foods is accumulating but, at present, there is limited evidence that they provide health benefits, although they may alter the gut microbiota in the short-term[13]. Positive evidence on yogurt consumption and health is largely driven by observational studies[14], which cannot determine cause and effect. There is, however, evidence that live cultures in yogurt can help support lactose digestion in those with lactose intolerance (because they lack the enzyme to break down this sugar).

While there is still a need for more research on specific interventions, it's clear that diets rich in fibre and plant food diversity – but not necessarily meat-free[15]– help to drive the gut microbiota towards more beneficial species. This is the type of diet we should be promoting regardless for general health and wellbeing.

*What we eat impacts on our microbiota – and there are opportunities for intervention as the microbiota isn't static and responds relatively quickly to dietary change.*

## DIETARY FIBRE, GUT MICROBIOTA COMPOSITION AND HEALTH

The theme of dietary fibre was developed further in the presentation by Prof. Kevin Whelan, Kings College London, which covered the following concepts:

- **Not all fibres are the same, so we need to be clear which fibre types we mean and the desired clinical outcomes;**
- **The terms 'soluble' and 'insoluble' are out-of-date as we've learnt more about the physicochemical properties of fibres;**
- **Fibre has a real impact on health and can potentially save lives;**
- **Some of the effects of fibre are modulated via the gut microbiota and short-chain fatty acids, but others are not;**
- **Individual responses to fibre differ and this is influenced by the gut microbiota.**

## EVOLVING DEFINITIONS OF FIBRE

The term 'fibre' is broader than we imagine, and this is reflected in changing definitions and guidelines, which have evolved over the years to include more types. Nowadays, 'fibre' encompasses all non-digestible carbohydrates with a degree of polymerisation ≥3 plus lignan and resistant starch[16]. Against a recommendation of 30g of fibre a day, adults in the UK eat just 19g on average, mostly from cereals (39%) and fruit/vegetables (29%)[10].

Interventions to improve fibre consumption have been based on different formats – supplements or natural foods – which is why it's problematic to take an overview of the health impact of fibre *per se*. There are pros and cons to each; while supplements may be lower cost and easier to comply with, they tend to narrow the fibre type and clinical effects. In contrast, natural fibre sources, e.g., dried fruits, wholegrains, vegetables, offer greater variety but may be expensive and unfamiliar to patients/consumers, which could lower compliance.

## FIBRE IS NOT ONE MOLECULE

Historic classification of fibre as 'soluble' and 'insoluble' is no longer relevant as we've learnt more about the physicochemical properties of different fibre types. A recent review found that solubility did not relate consistently to viscosity or fermentability, and a more complex view of physicochemical properties is required to predict the functional effects of increasing intake of individual fibres (see figure below)[17].

| PHYSIOCHEMICAL PROPERTIES | FUNCTIONAL PROPERTIES | EXAMPLE |
|---|---|---|
| SOLUBLE<br>VISCOUS<br>FERMENTABLE | NUTRIENT BIOAVAILABILITY<br>SCFA PRODUCTION | PECTIN, GALACTOMANNAN |
| SOLUBLE<br>NON-VISCOUS<br>FERMENTABLE | SCFA PRODUCTION<br>PREBIOTIC | INULIN, GOS |
| INSOLUBLE<br>NON-VISCOUS<br>NON-FERMENTABLE | FASTER TRANSIT<br>STOOL BULKING | CELLULOSE IN WHEAT BRAN |
| MEDIUM SOLUBILITY<br>MEDIUM VISCOSITY<br>LOW FERMENTABILITY | NUTRIENT BIOAVAILABILITY<br>FASTER TRANSIT<br>WATER HOLDING | PSYLLIUM |

Adapted from Gill SK *et al.* (2021) Nat Rev Gastroenterol Hepatol 18(2):101-116

As examples, pectin and psyllium have a similar viscosity and fermentability but pectin is soluble while psyllium is insoluble. Galacto-oligosaccharides (GOS) and alginates are both highly soluble but differ completely in their viscosity and fermentability.

The functional effects of fibre reach across the GI tract. In the small intestine, viscous fibres slow glucose and lipid absorption, and impact on glycaemic control and bile acid reabsorption. In the large intestine, psyllium limits mineral absorption while both psyllium and cellulose improve stool bulking and gut transit time. Fermentable fibres, e.g., inulin and GOS, have prebiotic effects and promote short-chain fatty acid (SCFA) production which has a range of metabolic effects in the body and brain.

## FIBRE AND HEALTH

The evidence is clear that eating more fibre reduces the risk of non-communicable diseases and improves life expectancy. The mechanisms involve a direct impact of fibre on the GI tract, e.g., stool bulking and transit time[18], as well as interactions between fibre and the gut microbiota which can improve gut barrier function and immunocompetency[19]. Prospective cohort trials[16] show that for every 7g of fibre eaten per day – equivalent to half a tin of baked beans or a baked potato – there is a:

- **9% lower risk of cardiovascular disease**
- **9% lower risk of heart attack**
- **7% lower risk of stroke**
- **6% lower risk of type 2 diabetes**

This is backed by randomised controlled trials on higher amounts of fibre showing short-term reductions in body weight, blood cholesterol, HbA1c and systolic blood pressure. Authorised health claims for fibre relate to faecal bulk, bowel function, gut transit time, and blood cholesterol and glucose levels, but not to modulating the gut microbiota as this is not considered by regulators to be a health outcome[20].

There is also evidence of benefit to clinical populations when fibre is increased, for example, ispaghula, psyllium and possibly linseed improve irritable bowel syndrome symptoms[21], while non-fermentable fibres, including sorbitol and psyllium, appear to be best for functional constipation[22].

## FIBRE AND THE GUT MICROBIOTA

Some of the health effects of fibre are modulated via changes to the gut microbiota and SCFA production. A cross-sectional study comparing people living in Italy versus Burkina Faso found a marked difference in the gut microbiota, with a higher ratio of Bacteroidetes to Firmicutes species seen in the African population – believed to represent a more favourable balance for health[23]. A randomised controlled trial revealed that bacterial diversity and levels of SCFA differed significantly when people followed a high fibre, plant-based diet versus a low fibre, animal-based diet, with the former delivering a more beneficial microbiota profile[24].

*An additional 7g of fibre in the diet is associated with a significant reduction in risk of 9% for cardiovascular disease, 9% for heart attack, 7% for stroke and 6% for type 2 diabetes.*

However, only certain types of fibre appear to have an impact on the gut microbiota. A systematic review and meta-analysis found that confirmed prebiotics, e.g., inulin and GOS, had a large effect on bifidobacteria (a beneficial species) while general fibres did not[25]. Interestingly, polydextrose and resistant starch had a lesser, but nevertheless statistically significant, effect on bifidobacteria, indicating that there are more prebiotics to discover.

Prebiotic consumption interacts with fibre consumption, according to a randomised controlled crossover trial which found that individual bacteria species, e.g., Lactobacillus or Faecalibacterium were enhanced or suppressed depending on habitual fibre intake[26]. Yet, reassuringly, prebiotics boosted levels of bifidobacteria regardless of baseline fibre levels.

The efficacy of fibre interventions also depends on the baseline gut microbiota. In a small acute intervention trial, participants who responded to a high fibre intervention with improved glycaemic control were found to have a particular gut microbiota pattern compared with non-responders[27]. When faecal samples from both groups were inoculated into germ-free mice, the animals' post-prandial glycaemic control mirrored that of the donors. This suggests there is something causal in the gut microbiota that can significantly impact on glucose metabolism.

In conclusion, fibre has variable definitions, molecules, interventions, physicochemical properties and functional characteristics, which means it also has differing effects on health and clinical outcomes. Hence, when communicating about fibre, it would be better to talk about the functional effects, for example stool bulking, glycaemic control or gut microbiota modulation, rather than whether a fibre is soluble or insoluble.

## EFFECTS OF PREBIOTIC CONSUMPTION ON GUT MICROBIOTA COMPOSITION AND HEALTH

The presentation by Dr Gemma Walton, University of Reading, delved further into prebiotics, defined in 2017 as "*selectively fermented ingredients that result in specific changes in the composition and/or activity of the GI microbiota, thus conferring benefit(s) upon host health*"[28]. She also covered:

- **How the gut microbiota changes as people age;**
- **Interactions between the microbiota, immune system and chronic disease risk;**
- **The potential role for prebiotics in infants and elderly populations;**
- **Models for investigating the impact of prebiotics on health;**
- **Future directions for prebiotics research.**

## INTRODUCING PREBIOTICS

The definition states clearly what criteria needs to be met in order to call something a prebiotic – a dietary ingredient that persists in the GI tract and stimulates growth of positive bacteria, for example lactobacilli or bifidobacteria, and, most importantly, it must confer a measurable health advantage.

Prebiotics are thought to work through a chain of events that begins with selective fermentation by beneficial bacteria which, by thriving, inhibit the establishment of less favourable species. The 'good' bacteria combined with increased levels of fermentable dietary ingredient tend to result in increased SCFA and lower the pH of the colon which, in turn, creates an even more favourable environment for the target species.

The metabolic activities of beneficial species, such as SCFA production and mucus production, drive changes to innate immunity by strengthening the gut barrier and its tight junctions – vital for keeping out pathogens – as well as enhancing adaptive immunity through effects on T-helper cells, cytokine production and the inflammatory response.

## POTENTIAL FOR PREBIOTICS IN AGING

Human populations in developed countries, such as the UK, are getting older but not healthier. While longevity has continued to creep upwards by 2.7 years every decade on average, the years spent in good health have not kept pace. Data from the Office of National Statistics[29] reveal that disability-free life expectancy was 62.3 years for men and 61.0 years for women in 2017-19 and had declined in females since 2014-16. This is against a life expectancy of 79 years in men and 83 years in women – that's around 20 years of life typically spent in ill health.

*Microbiota diversity declines with old age and is associated with increased frailty and inflammation, as well as age-related decline in the immune response.*

Aging is acknowledged as the single most important risk factor for major chronic diseases, but it also affects the gut microbiota. Between birth and old age, the gut microbiota evolves in response to different circumstances, for example whether we had a vaginal or Caesarean birth, whether we were breast or formula fed, when we were weaned and onto which foods, as well as our disease experience and dentition in later life. bifidobacteria – the predominant genera in infanthood linked to SCFA production and positive immune effects – decline in childhood and adulthood and further on reaching old age, with the greatest reductions seen in people aged over 100 years[30].

Microbial changes including reduced diversity[31] occur with advancing biological age and is associated with frailty[32]. The gut of elderly people tends to have lower numbers of important SCFA producers, such as ruminococci and clostridia cluster XIV, and more protein breakdown (proteolysis) which has been linked to negative effects on cell turnover. Higher colon protein degradation may explain the increasing risk of colonic cancer with advancing age.

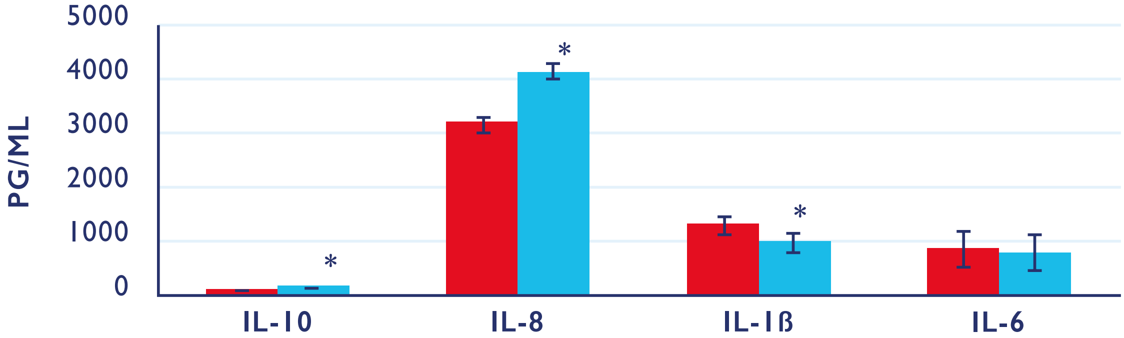
These gut microbiota changes are likely to be a factor in the development of immunosenescence – age-related decline in the immune response – which is characterised by a decline in T-cell function, reductions in B-cells and natural killer cells, impaired antigen presenting and chronic inflammation. The overall effect is a decline in the capacity of the immune system to respond appropriately to pathogens or, indeed, vaccines. Inflammation is a problem as it has been independently

## HUMAN STUDIES ACROSS THE AGE DIVIDE

Prebiotics can address some of the gut microbiota issues seen in older populations and one way of studying this is to use the in vitro method of anaerobic faecal batch culture fermenters. In one study at the University of Reading, faecal samples from three donors were cultured with two different prebiotics, inulin (1%) and GOS, versus a control. The results showed that both prebiotics boosted levels of bifidobacteria species along with levels of acetate. When human peripheral blood mononuclear cells were added to samples of the different fermentation cultures and 'challenged' using bacterial lipopolysaccharide, those exposed to prebiotics responded with lower levels of inflammation (TNF-α) and higher anti-inflammatory cytokines. These activities against inflammations would be positive in real life in ageing when chronic inflammation is increasing.

The concept was tested further in a group of 40 older adults supplemented with GOS (2.75g daily) or a placebo for 10 weeks[33]. The randomised controlled crossover study showed an increase in bifidobacteria in faecal samples and an overall positive change in microbial balance. Cytokine production was significantly altered to a less inflammatory profile with higher levels of immune-supporting IL-8 and natural killer cells (see figure below).

### CYTOKINE MODULATION




| | IL-10 | IL-8 | IL-1ß | IL-6 |
|---|---|---|---|---|
| PLACEBO | 62 | 3171 | 1281 | 832 |
| B-GOS | 114 | 4140 | 954 | 776 |

Adapted from Vulevic J *et al.* (2015) Br J Nutr 114: 586-95

At the other end of the lifecycle, prebiotics were tested in 259 healthy formula-fed infants with a familial risk of allergy. The 6-month intervention trial compared GOS+inulin or a maltodextrin control and followed up the children at 2 years and 5 years[34]. The results showed increased bifidobacteria populations but no difference in lactobacilli when prebiotics and controls were compared. More importantly, there was a significant reduction in allergy, atopic dermatitis and rhino-conjunctivitis.

## FUTURE DIRECTIONS

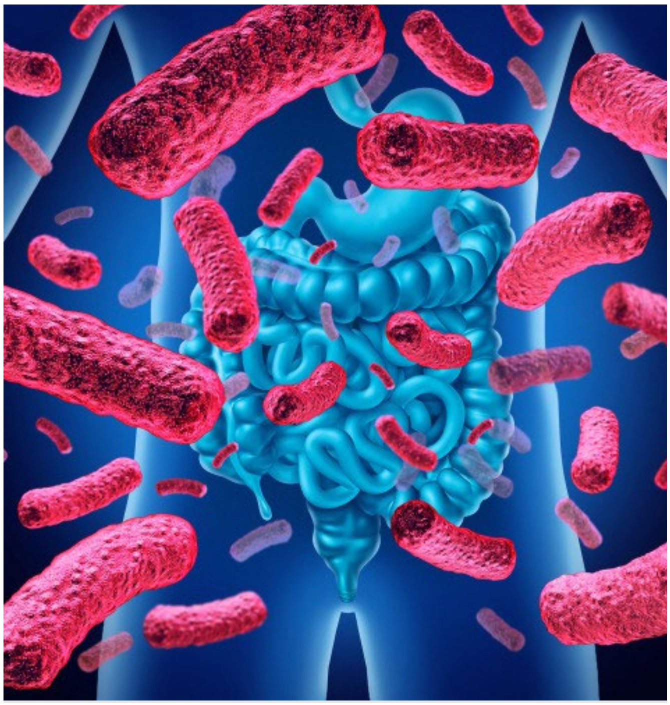
Studies on prebiotics have so far examined their role in stool frequency, metabolic health, immune function in adults and children, travellers' diarrhoea, irritable bowel syndrome and vaccine response – with many positive outcomes. The potential for prebiotics to modulate the gut-brain axis is an exciting future area of study. Animal models suggest that stress can shift the balance of gut microbiota towards less favourable species. Stress is also linked with inflammation – which also has a detrimental impact on gut microbiota and immune health. Certain species of gut bacteria are known to produce neuroactive metabolites, such as serotonin or gamma amino butyric acid (GABA) that can impact on brain health and potentially behaviour and mood. Observational studies reveal that mood disorders, such as depression, are associated with a particular less favourable profile of gut microbiota. It is, therefore, a short step towards hypothesising that modulating the gut microbiota could impact on mood disorders – but this is yet to be properly investigated.

In conclusion, to return to the original definition of prebiotics, it is not enough to show gut microbiota modulation as positive, health effects are also required. Many products have strong evidence in this direction, but worth bearing in mind for new novel emerging prebiotics.

## THE RELATIONSHIP BETWEEN PROBIOTICS AND THE MICROBIOME

The Yakult study day now turned to probiotics which have been the subject of an explosion in interest, with more than 29,000 studies recorded up to 2020. Prof. Colin Hill, University College Cork, considered the following in his presentation:

- **Exploring how probiotics interact with the microbiota;**
- **The importance of establishing efficacy;**
- **Effects of probiotics with a focus on infection prevention;**
- **Potential use of next generation probiotics in medicine**
- **Future directions for prebiotics research**



## INTRODUCING PROBIOTICS

It is worth being clear about the shared and differing features of probiotics versus the microbiota – summarised below – since these terms are used frequently in studies.

| Probiotics | Microbiota |
|---|---|
| Living microbes | |
| Can be a source of probiotics | |
| Provide a health benefit | |
| Numbering ~$10^9$ | Numbering ~$10^{14}$ |
| Delivered to body site | Present in the body site |
| Highly characterised and typically species-specific | Highly complex and diverse |
| Short-term exposure | Long-term residence |

The microbiota should be seen as the stage on which probiotics, prebiotics and other gut modulators act. Probiotics are at a relative disadvantage when attempting to establish themselves in the body since they are around 5 log smaller in number compared with the microbiota. Yet, probiotics do not have to colonise the host, or have a long-lasting impact on microbiota composition or functionality to deliver a benefit – they may simply offer health effects in passing. This needs to be acknowledged as some academics have stated incorrectly that probiotics are not worth taking because they don't colonise the host[35].

There are now several important consensus statements – all open access – that define the scope and appropriate use of the terms **fermented foods**, **probiotic**, **prebiotic**, **synbiotic** and **postbiotic**[28,36-39]. These statements are clear that, for something to be called a probiotic, confirmation of efficacy in humans is essential. Yet, to meet the criteria for a probiotic definition, there is no requirement for a mechanism to be elucidated.

## WHAT DO PROBIOTICS DO?

The vast literature on probiotics shows that many different types of probiotics have effects on gut barrier reinforcement, normalisation of dysbiosis, acid and SCFA production, regulation of intestinal transit and competitive exclusion of pathogens. Specific genus or species have been observed to influence vitamin synthesis, bile salt metabolism and enzymatic activity, and exhibit anti-carcinogenic and anti-inflammatory effects. In contrast, few specific strain effects are seen in studies, but these may include neurological or endocrinological effects, and production of specific bioactives. Some probiotics have multiple effects across health outcomes.

*Probiotics should be seen as tourists, not residents. They don’t have to colonise the host or alter the gut microbiome to have positive health effects.*

A large systematic review and meta-analysis of 74 studies and 84 trials involving more than 10,000 patients examined the impact of probiotics on GI diseases[40]. The authors concluded that: “across all diseases and probiotic species, positive significant effects of probiotics were observed for all age groups, single vs. multiple species, and treatment lengths”. This shows that probiotics are beneficial for the treatment and prevention of GI diseases.

Another meta-analysis[41] looked specifically at diarrhoea, finding that probiotics significantly reduced antibiotic-associated diarrhoea by 52%, travellers’ diarrhoea by 8% and acute diarrhoea of diverse causes by 34%. The same study identified that probiotics reduced the risk of acute diarrhoea by 57% in children and by 26% in adults.

Genera and strain are important for some, but not all, health impacts. By conducting a meta-analysis of the different probiotic strains used to prevent hospital-acquired diarrhoeal disease, an ESPGHAN Working Group determined that Lactobacillus rhamnosus GG should be recommended in children[42].

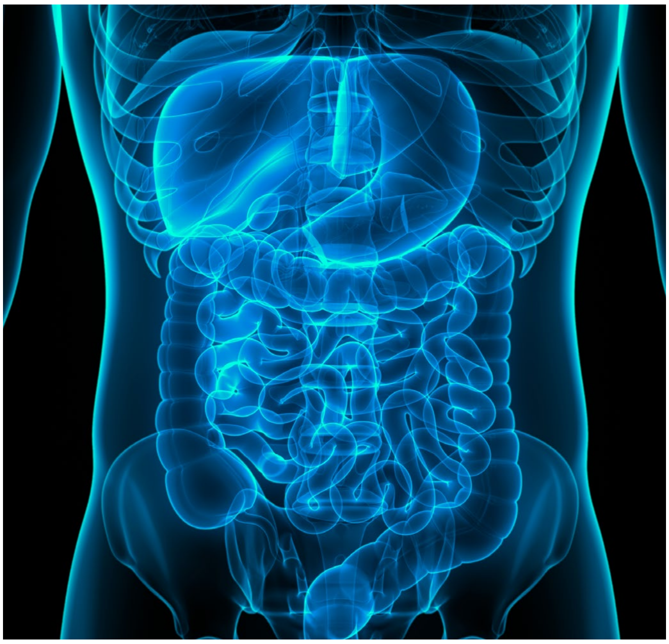
## HOW DO PROBIOTICS WORK?

Probiotics can impact on host health via three main access points; (1) through dietary components by producing metabolites such as SCFA; (2) through the microbiome by creating a favourable environment for beneficial species by lowering gut lumen pH; or (3) acting directly on the host e.g., by acting on the gut-brain axis.

Probiotics produce a number of effector molecules such as bacteriocins, enzymes, metabolites and bacteriophage which directly interact with the host[43]. Effector molecules and their actions may be strain specific as demonstrated by mouse models of listeria infection[44] and studies of gene regulatory responses in human GI tract cells exposed to different lactobacillus strains[45]. The probiotic biomass itself can be an effector as demonstrated by a study where a heat-treated lactobacillus strain (a so-called 'postbiotic') was able to modulate the GI microbiota and colitis in a mouse model[46].

Probiotics can help prevent infection by killing/inhibiting pathogens, making the gut environment more hostile to pathogens, or by strengthening host defences by producing mucus, modulating immune function and improving the gut barrier.

Human trials have demonstrated this in practice. In a randomised controlled trial of a synbiotic (*L. plantarumand* + fructooligosaccharide) in 4,556 infants in rural India, there was a significant 40% reduction in death and neonatal sepsis in the infants receiving the synbiotic. Lower respiratory tract infections were also reduced.



## MICROBIOME SHIFTS

The microbiome evolves from birth to old age as previously described but evidence suggests that dysbiosis, marked by less diversity, occurs at times of ill health, for example when elderly people become frail and require care[47] or when people develop inflammatory bowel disease.

We have many microbiomes apart from the GI tract, e.g., skin, vagina, lungs. When considering the efficacy of probiotics, it's important to know where the probiotic is likely to act as the microbiota of the small intestine has far lower numbers and diversity of bacteria compared with that of the distal colon. This explains why the effect of probiotics tends to dilute as they travel through the GI tract.

The impact of probiotics in the gut can relate to increased SCFA production – as demonstrated by a 4-week study in adults using *L. plantarum*[48] or both species and SCFA changes as shown in a study in overweight children[49] using *L. paracasei* Shirota. Neither of these studies tested for health outcomes.

The next generation of probiotics could involve genetic modification of existing species, or new species developed to target particular medical applications[50]. Emerging evidence suggests that having a particular microbiome can influence the response to immunotherapy for cancer treatment which could have huge implications for human health.

In conclusion, probiotics have a positive impact on human health but don't necessarily act by changing our gut microbiome or its functionality, although some clearly do. The microbiome provides the setting where host, food (e.g., prebiotics) and probiotics meet. Probiotics can be viewed as tourists which have passing beneficial effects, particularly in the small intestine where they are able to dominate the microbiota.

## CONCLUSION

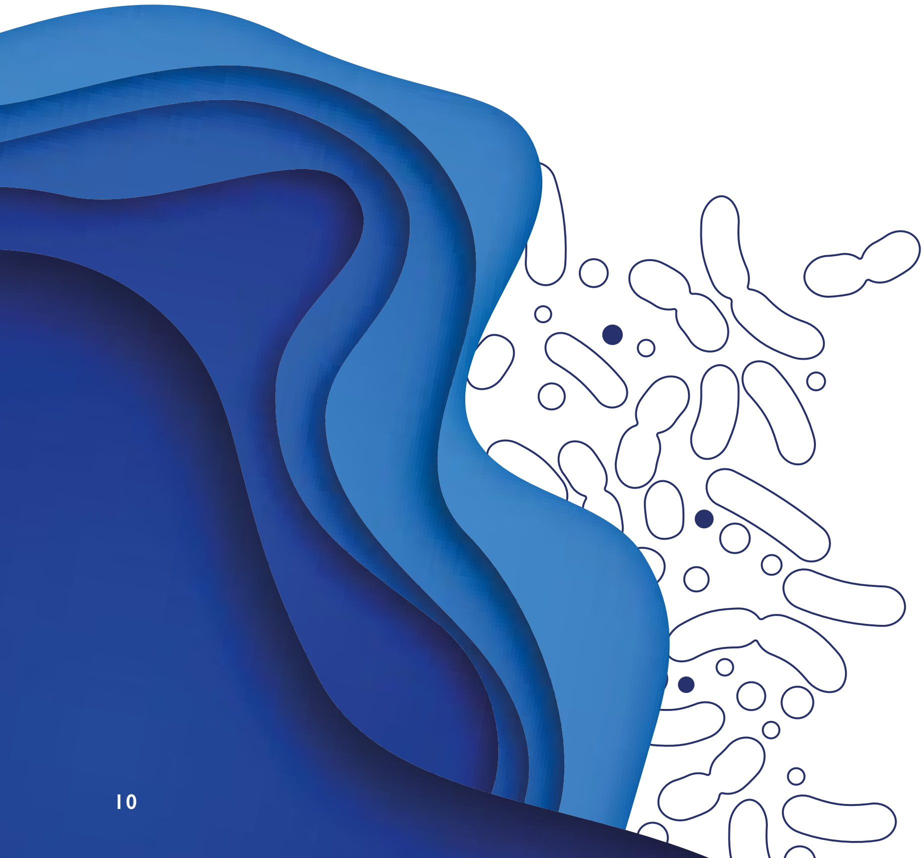
The overall conclusions of the Yakult study day are:

- **There is increasing consumer interest in gut health modulators, such as probiotics, prebiotics and fermented foods. Hence, it is important for healthcare professionals to keep abreast of the literature and be aware of changing clinical guidelines.**

- **Eating more fibre is one way to improve the gut microbiota and leverage health effects, such as reduced risk of chronic disease. However, fibre is not one molecule, and we need to be clear which fibre type is appropriate for the clinical outcome required.**

- **Prebiotics are a type of fibre and are backed by a growing body of evidence across the age divide. There are interesting applications for the use of prebiotics in elderly populations which tend to see an age-related decline in microbiota diversity linked to immunosenescence.**

- **Probiotics are also proven to impact on health and may do this by modulating the existing microbiota, altering functionality or by acting directly on the host. Probiotics have interesting potential for lowering infection risk in adults and children and the next generation of probiotics could have medical applications.**



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