Role of the gut microbiota in nutrition and health

Ana M Valdes and colleagues discuss strategies for modulating the gut microbiota through diet and probiotics

Microbiome refers to the collective genomes of the micro-organisms in a particular environment, and microbiota is the community of micro-organisms themselves (box 1). Approximately 100 trillion micro-organisms (most of them bacteria, but also viruses, fungi, and protozoa) exist in the human gastrointestinal tract[1] [2]—the microbiome is now best thought of as a virtual organ of the body. The human genome consists of about 23 000 genes, whereas the microbiome encodes over three million genes producing thousands of metabolites, which replace many of the functions of the host,[1 3] consequently influencing the host's fitness, phenotype, and health.[2]

Studying the gut microbiota

Twin studies have shown that, although there is a heritable component to gut microbiota, environmental factors related to diet, drugs, and anthropometric measures are larger determinants of microbiota composition.[4 5]

Gut microbes are key to many aspects of human health including immune,[6] metabolic[5] and neurobehavioural traits (fig 1).[7 8] Different levels of evidence support the role of gut microbiota in human health, from animal models[9 10] and human studies.[4 11-13]

Animal models can help identify gut microbes and mechanisms, though the degree to which findings translate to humans is unknown. In humans, observational studies can show cross-sectional associations between microbes and health traits but are limited by the inability to measure causal relations. The strongest level of evidence is obtained from interventional clinical studies—in particular, randomised controlled trials.

The composition of gut microbiota is commonly quantified using DNA based methods, such as next generation sequencing of 16S ribosomal RNA genes or whole genome shotgun sequencing,

Box 1: Glossary

- *Microbiome*—the collective genomes of the micro-organisms in a particular environment
- *Microbiota*—the community of micro-organisms themselves
- *Microbiota diversity*—a measure of how many different species and, dependent on the diversity indices, how evenly distributed they are in the community. Lower diversity is considered a marker of dysbiosis (microbial imbalance) in the gut and has been found in autoimmune diseases and obesity and cardiometabolic conditions, as well as in elderly people
- *Operational taxonomic unit*—a definition used to classify groups of closely related organisms. DNA sequences can be clustered according to their similarity to one another, and operational taxonomic units are defined based on the similarity threshold (usually 97% similarity) set by the researcher
- *Colonocytes*—epithelial cells of the colon
- *Germ-free animals*—animals that have no micro-organisms living in or on them
- *Short chain fatty acids*—fatty acids with two to six carbon atoms that are produced by bacterial fermentation of dietary fibres

KEY MESSAGES

- Gut microbiota influences many areas of human health from innate immunity to appetite and energy metabolism
- Targeting the gut microbiome, with probiotics or dietary fibre, benefits human health and could potentially reduce obesity
- Drugs, food ingredients, antibiotics, and pesticides could all have adverse effects on the gut microbiota
- Microbiota should be considered a key aspect in nutrition; the medical community should adapt their education and public health messages
- Fibre consumption is associated with beneficial effects in several contexts
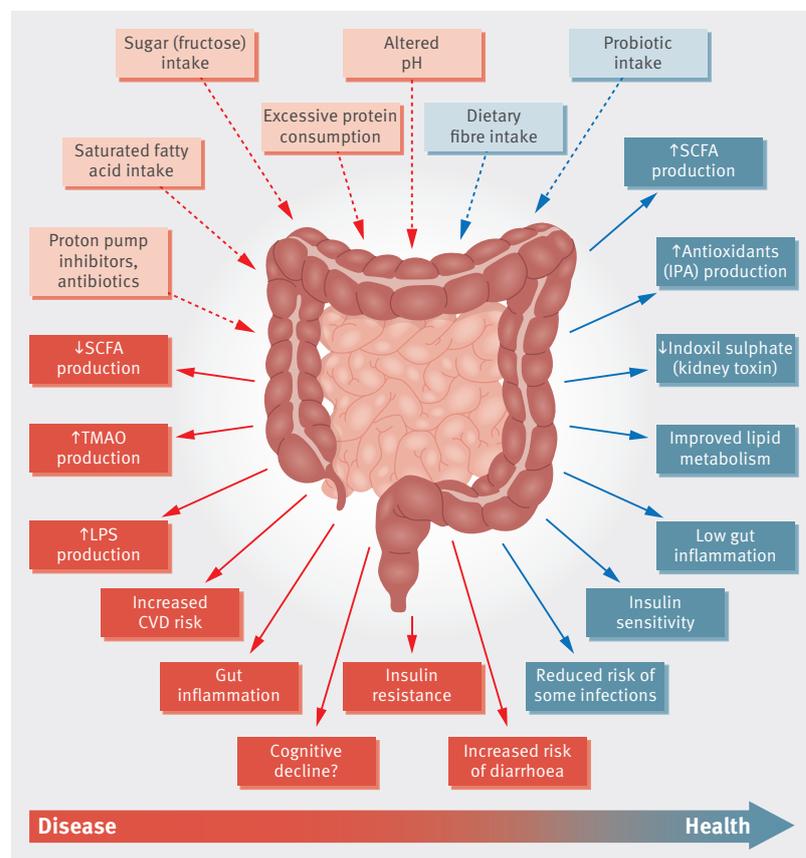

Fig 1 | Schematic representation of the role of the gut microbiota in health and disease giving some examples of inputs and outputs. CVD=cardiovascular disease; IPA=indolepropionic acid; LPS=lipopolysaccharide; SCFA=short chain fatty acids; TMAO=trimethylamine N-oxide

which also allow inference of microbiota functions.[14][15] Metabolic products of the microbiota are now measurable in stool and serum using metabolomic methods.[16]

What does the gut microbiota do?

The gut microbiota provides essential capacities for the fermentation of non-digestible substrates like dietary fibres and endogenous intestinal mucus. This fermentation supports the growth of specialist microbes that produce short chain fatty acids (SCFAs) and gases.[17] The major SCFAs produced are acetate, propionate, and butyrate.

Butyrate is the main energy source for human colonocytes, can induce apoptosis of colon cancer cells, and can activate intestinal gluconeogenesis, having beneficial effects on glucose and energy homeostasis.[18] Butyrate is essential for epithelial cells to consume large amounts of oxygen through β oxidation, generating a state of hypoxia that maintains oxygen balance in the gut, preventing gut microbiota dysbiosis.[19]

Propionate is transferred to the liver, where it regulates gluconeogenesis and satiety signalling through interaction with the gut fatty acid receptors [18] Acetate—the most abundant SCFA and an essential metabolite for the growth of other bacteria—reaches the peripheral tissues where it is used in cholesterol metabolism and lipogenesis, and may play a role in central appetite regulation.[20] Randomised controlled trials have shown that higher production of SCFAs correlates with lower diet-induced obesity[21] and with reduced insulin resistance.[22] Butyrate and propionate, but not acetate, seem to control gut hormones and reduce appetite and food intake in mice.[21] Gut microbial enzymes contribute to bile acid metabolism, generating unconjugated and secondary bile acids that act as signalling molecules and metabolic regulators to influence important host pathways.[23]

Other specific products of the gut microbiota have been implicated directly in human health outcomes. Examples include trimethylamine and indolepropionic acid. The production of trimethylamine from dietary phosphatidylcholine and carnitine (from meat and dairy) depends on the gut microbiota and thus its amount in blood varies between people. Trimethylamine is oxidised in the liver to trimethylamine N-oxide, which is positively associated with an increased risk of atherosclerosis and major adverse cardiovascular events.[24] Indolepropionic acid is highly correlated with dietary fibre intake[25] and has potent radical scavenging activity in vitro,[26] which seems to reduce the risk of incidence of type 2 diabetes.[25]

The gut microbiota and obesity

The gut microbiota seems to play a role in the development and progression of obesity. Most studies of overweight and obese people show a dysbiosis characterised by a lower diversity.[31-39] Germ-free mice that receive faecal microbes from obese humans gain more weight than mice that receive microbes from healthy weight humans.[4] A large study of UK twins found that the genus *Christensenella* was rare in overweight people and when given to germ free mice prevented weight gain.[4] This microbe and others such as *Akkermansia* correlate with lower visceral fat deposits.[12] Although much of the confirmatory evidence comes from mouse models, long term weight gain (over 10 years) in humans correlates with low microbiota diversity, and this association is exacerbated by low dietary fibre intake.[28]

Gut microbiota dysbiosis probably promotes diet induced obesity and metabolic complications by a variety of mechanisms including immune dysregulation, altered energy regulation, altered gut hormone regulation, and proinflammatory mechanisms (such as lipopolysaccharide endotoxins crossing the gut barrier and entering the portal circulation[29][30]; fig 1).

Microbiota diversity and health

Lower bacterial diversity has been reproducibly observed in people with inflammatory bowel disease,[31] psoriatic arthritis,[32] type 1 diabetes,[33] atopic eczema,[34] coeliac disease,[35] obesity,[36] type 2 diabetes,[37] and arterial stiffness,[38] than in healthy controls. In Crohn's disease smokers have even lower gut microbiome diversity.[39] The association between reduced diversity and disease indicates that a species-rich gut ecosystem is more robust against environmental influences, as functionally related microbes in an intact ecosystem can compensate for the function of other missing species. Consequently, diversity seems to be a generally good indicator of a "healthy gut."[40][41] But recent interventional studies indicate that major increases in dietary fibre can temporarily reduce diversity, as the microbes that digest fibre become specifically enriched, leading to a change in composition and, through competitive interactions, reduced diversity.[22]

The functional role of the gut microbiome in humans has been shown using faecal microbiota transplantation.[42] This procedure is effective in cases of severe drug refractory *Clostridium difficile* infection and is now routinely used for this purpose around the world.[43] For other pathologies, faecal transplants are not yet clinical practice but have been explored.[44] For example, transplanting faeces from a lean healthy donor (allogeneic) to recipients

with metabolic syndrome resulted in better insulin sensitivity, accompanied by altered microbiota composition, than using autologous faeces.[45]

Effects of food and drugs on the gut microbiota

Specific foods and dietary patterns can all influence the abundance of different types of bacteria in the gut, which in turn can affect health (table 1).

High-intensity sweeteners are commonly used as sugar alternatives, being many times sweeter than sugar with minimal calories. Despite being "generally recognised as safe" by regulatory agencies, some animal studies have shown that these sugar substitutes may have negative effects on the gut microbiota.[46] Sucralose, aspartame, and saccharin have been shown to disrupt the balance and diversity of gut microbiota.[46] Rats given sucralose for 12 weeks had significantly higher proportions of *Bacteroides*, *Clostridia*, and total aerobic bacteria in their guts and a significantly higher faecal pH than those without sucralose.[47] Mice given sucralose for six months had an increase in the expression in the gut of bacterial pro-inflammatory genes and disrupted faecal metabolites.[48]

Food additives, such as emulsifiers, which are ubiquitous in processed foods, have also been shown to affect the gut microbiota in animals.[49] Mice fed relatively low concentrations of two commonly used emulsifiers—carboxymethylcellulose and polysorbate-80—showed reduced microbial diversity compared with mice not fed with emulsifiers. Bacteroidales and Verrucomicrobia were decreased and inflammation promoting Proteobacteria associated with mucus was enriched.[49]

Other areas of concern include the side effects of popular restrictive diets on gut health. These include some strict vegan diets, raw food or "clean eating" diets, gluten-free diets, and low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diets used to treat irritable bowel syndrome.

Vegans are viewed by some as healthier than omnivores. A study of 15 vegans and 16 ominvores found striking differences in serum metabolites generated by the gut microbes but very modest differences in gut bacterial communities.[50] A controlled feeding experiment of 10 human omnivores randomised to receive either a high fat and low fibre diet or a low fat and high fibre for 10 days found very modest effects on gut microbiome composition and no difference in short chain fatty acid production. Together these data support a greater role for diet influencing the bacterial derived metabolome than just the short term bacterial community.[50]

Table 1 | Examples of foods, nutrients, and dietary patterns that influence human health linked to their effect on the gut microbiota

Dietary element	Effect on gut microbiome	Effect on health outcomes mediated by gut microbiome	Human observational studies	Human interventional studies
Low FODMAP diet	Low FODMAP diet increased Actinobacteria; high FODMAP diet decreased abundance of bacteria involved in gas consumption[58]	Reduced symptoms of irritable bowel syndrome[56]	Yes	Yes
Cheese	Increased *Bifidobacteria*,[97 98] which are known for their positive health benefits to their host through their metabolic activities.[99] Decrease in *Bacteroides* and *Clostridia*, some strains of which are associated with intestinal infections[98]	Potential protection against pathogens.[100] Increased production of SCFA and reduced production of TMAO[99]	Yes	Yes
Fibre and prebiotics	Increased microbiota diversity and SCFA production[22 101 102]	Reduced type 2 diabetes[22] and cardiovascular disease[103]	Yes	Yes
Artificial sweeteners	Overgrowth of Proteobacteria and *Escherichia coli*.[104] *Bacteroides*, *Clostridia*, and total aerobic bacteria were significantly lower, and faecal pH was significantly higher[47]	Induced glucose intolerance[105]	No	No
Polyphenols (eg, from tea, coffee, berries, and vegetables such as artichokes, olives, and asparagus)	Increased intestinal barrier protectors (*Bifidobacteria* and *Lactobacillus*), butyrate producing bacteria (*Faecalibacterium prausnitzii* and *Roseburia*) and *Bacteroides vulgatus* and *Akkermansia muciniphila*.[107] Decreased lipopolysaccharide producers (*E coli* and *Enterobacter cloacae*)[106]	Gut micro-organisms alter polyphenol bioavailability resulting in reduction of metabolic syndrome markers and cardiovascular risk markers[108]	Yes	Yes
Vegan	Very modest differences in composition and diversity in humans and strong differences in metabolomic profile compared with omnivore diet in humans[50]	Some studies show benefit of vegetarian over omnivore diet,[109] others fail to find a difference[110]	Yes	Yes

FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides and polyols; SCFA=small chain fatty acids; TMAO= trimethylamine N-oxide

Animal and in vitro studies indicate that gluten-free bread reduces the microbiota dysbiosis seen in people with gluten sensitivity or coeliac disease.[51 52] But most people who avoid gluten do not have coeliac disease or proved intolerance, and a recent large observational study showed an increased risk of heart disease in gluten avoiders, potentially because of the reduced consumption of whole grains.[53] One study showed that 21 healthy people had substantially different gut microbiota profiles after four weeks on a gluten-free diet. Most people showed a lower abundance of several key beneficial microbe species.[54]

The low FODMAP diet has been shown in six randomised controlled trials to reduce symptoms of irritable bowel syndrome.[55 56] It is associated with a reduced proportion of *Bifidobacterium* in patients with irritable bowel syndrome, and responsiveness to this diet can be predicted by faecal bacterial profiles.[57] Low FODMAP diets lead to profound changes in the microbiota and metabolome, the duration and clinical relevance of which are as yet unknown.[58 59]

In addition to diet, medication is a key modulator of the gut microbiota composition. A large Dutch-Belgian population study showed that drugs (including osmotic laxatives, progesterone, TNF-☐ inhibitors and rupatadine) had the largest explanatory power on microbiota composition (10% of community variation).[13] Other studies have shown major effects of commonly prescribed proton pump inhibitors on the microbial community, which could explain higher rates of gastrointestinal infection in people taking these drugs.[60] Antibiotics clearly have an effect on gut microbes, and low doses are routinely given to livestock to increase their growth and weight. A large proportion of antibiotic use in many countries is for agriculture—particularly intensive farming of poultry and beef.[61] Several observational human studies as well as many rodent studies have pointed to an obesogenic effect of antibiotics in humans even in tiny doses found in food.[61] But humans have very variable responses to antibiotics, and intervention studies have not shown consistent metabolic consequences.[62] Pesticides and other chemicals are commonly sprayed on foods, but, although levels can be high, solid evidence for their harm on gut health and the effects of organic food is currently lacking.[63]

Insufficient clinical evidence exists to draw clear conclusions or recommendations for these or other dietary preferences based on gut microbiota. But future studies of food additives, drugs, and the safety and efficacy of dietary modifications must take into account these advances and their effect on the gut microbiota. This is becoming clear in patients with cancer treated with immunochemotherapy, bone marrow recipients, and patients with autoimmune disorders on biologics, where small changes in their microbiota can cause major changes in their response.[64] Moreover, animal experiments have shown the protective effects of phytoestrogens on breast cancer depend on the presence of gut microbes (such as *Clostridium saccharogumia, Eggerthella lenta, Blautia producta,* and *Lactonifactor longoviformis)* that can transform isoflavones into the bioactive compounds.[65]

Box 2 summarises our current knowledge on the interactions between gut microbiota, nutrition, and human health.

Box 2: Consensus and uncertainties

What we know

- Probiotic supplementation has several beneficial effects on human health
- The microbes in our gut influence and human energy metabolism[22-45]
- Diet and medication have a strong influence on gut microbiota composition
- Microbiota composition influences response to chemotherapy and immunotherapy[96]
- Microbiome composition defines glucose response to foods and can be used to personalise diet[94]
- Dietary fibre intake influences gut microbiota composition and is related to better health[86 87 104]

What we don't know

- Are natural probiotics in food better than probiotic supplements? Should we take them preventively?
- Can microbes influence food choices and appetite?
- Do low dose antibiotics in food affect human health?
- What is the effect of pesticides in food on the gut microbiome? Is organic food better for the gut microbiota?
- Should all new drugs and food chemicals be tested on the gut microbiota?

Manipulating the gut microbiota through diet

Changes to the gut microbiota can occur within days of changing diet; remarkable differences were found after African Americans and rural Africans switched diets for only two weeks.[66] Increased abundance of known butyrate producing bacteria in the African Americans consuming a rural African diet caused butyrate production to increase 2.5 times and reduced synthesis of secondary bile acid.[66] Another study comparing extreme shifts between plant and animal protein based diets showed these changes after only five days.[67] But healthy microbiota are resilient to temporal changes by dietary interventions, meaning that homeostatic reactions restore the original community composition, as recently shown in the case of bread [68]

Prebiotic foods and dietary fibre

Most national authorities define dietary fibre as edible carbohydrate polymers with three or more monomeric units that are resistant to the endogenous digestive enzymes and thus are neither hydrolysed nor absorbed in the small intestine.[69] A subset of dietary fibre sources is fermentable, which means that they serve as growth substrates for microbes in the distal bowel.[70] Some non-digestible carbohydrates have been referred to as "prebiotics," which are defined as food components or ingredients that are not digestible by the human body but specifically or selectively nourish beneficial colonic micro-organisms (box 3).[71] The prebiotic concept has been criticised for being poorly defined and unnecessarily narrow,[72] and some scientists prefer the term "microbiota accessible carbohydrates,"[11] which are essentially equivalent to fermentable dietary fibre in that they become available as growth substrates for gut microbes that possess the necessary enzymatic capacity to use them.[70]

Consuming resistant starches has been shown to enrich specific bacterial groups (*Bifidobacterium adolescentis, Ruminococcus bromii*, and *Eubacterium rectale*) in some people.[74 75] The taxa enriched differ depending on the type of resistant starches and other dietary fibres,[75] indicating that shifts are dependent on the carbohydrate's chemical structure and the microbes' enzymatic capacity to access them. Microbes need also to "adhere" to a substrate and tolerate the conditions generated from fermentation (such as low pH).[76]

The effect of microbiota accessible carbohydrates on the gastrointestinal microbiome composition can be substantial, with specific species becoming enriched to constitute more than 30% of the faecal microbiota.[75 77] Thus, microbiota accessible carbohydrates provide a potential strategy to enhance useful minority members of the microbiome. These changes only last as long as the carbohydrate is consumed, and they are highly individual, which provides a basis for personalised approaches. Many short term feeding trials with purified dietary fibres or even whole plant based diets either have no effect on microbiota diversity or reduce it,[22] but can still have clinical benefits, potentially through metabolites such as small chain fatty acids.[22 67]

Low fibre intake reduces production of small chain fatty acids and shifts the gastrointestinal microbiota metabolism to use less favourable nutrients,[78] leading to the production of potentially detrimental metabolites.[79 80] Convincing evidence shows that the low fibre Western diet degrades the colonic mucus barrier, causing microbiota encroachment, which results in pathogen susceptibility[81] and inflammation,[82] providing a potential mechanism for the links of Western diet with chronic diseases. Two recent studies showed that the detrimental effects of high fat diets on penetrability of the mucus layer and metabolic functions could be prevented through dietary administration of inulin.[83] [84] Overall, these findings, together with the role of butyrate in preventing oxygen induced gut microbiota dysbiosis,[19] provide a strong rational to enrich dietary fibre consumption to maintain intact mucosal barrier function in the gut.[85]

Considerable observational evidence shows that fibre intake is beneficial for human health. Two recent meta-analyses found clear links between dietary fibre and health benefits in a wide range of pathologies,[86 87] and a recent intervention study found dietary fibres significantly reduced insulin resistance in patients with type 2 diabetes, with clear links to the shifts in the microbiota and beneficial metabolites (such as butyrate).[45]

Probiotic foods

Probiotics are live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host).[88] Probiotics (mostly *Bifidobacterium* and *Lactobacillus* species) can be included in a variety of products, including foods, dietary supplements, or drugs.

There are concerns that most microbe supplements are unable to establish themselves in the gut and fail to exert an effect on the resident community.[89 90] But probiotics can affect health independently of the gut microbiota through direct effects on the host; for example, through immune modulation or the production of bioactive compounds. The therapeutic effect of probiotic supplementation has been studied in a broad range of diseases.

We searched the Cochrane library of systematic reviews for "probiotic*", yielding 39 studies, and searched Medline for "systematic review" or "meta-analysis" and "probiotic*", yielding 31 studies. We included information on systematic reviews of randomised controlled trials published in the past five years where the main treatment was probiotics (not dietary supplements in general). Only studies that focused on comparisons of probiotics with a control group, that contained at least some moderate or high quality randomised controlled trials in the estimation of the authors of the systematic review, which resulted in a total of 22 systematic reviews (table 2). The analysis of 313 trials and 46 826 participants showed substantial evidence for beneficial effects of probiotic supplementation in preventing diarrhoea, necrotising enterocolitis, acute upper respiratory tract infections, pulmonary exacerbations in children with cystic fibrosis, and eczema in children. Probiotics also seem to improve cardiometabolic parameters and reduced serum concentration of C reactive protein in patients with type 2 diabetes. Importantly, the studies were not homogeneous and were not necessarily matched for type or dose of probiotic supplementation nor length of intervention, which limits precise recommendations. Emerging areas of probiotic treatment include using newer microbes and combinations, combining probiotics and prebiotics (synbiotics),[91] and personalised approaches based on

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Box 3: What are prebiotics and probiotics?

Dietary amounts of protein, saturated and unsaturated fats, carbohydrates, and dietary fibre influence the abundance of different types of bacteria in the gut. The microbiota can also be modified by adding live micro-organisms to food or by periods of fasting.

- Probiotics are live bacteria and yeasts that, when administrated in a viable form and in adequate amounts, are beneficial to human health. They are usually added to yoghurts or taken as food supplements.
- Prebiotics are defined as a substrate that is selectively used by host micro-organisms conferring a health benefit. Although all compounds considered prebiotics are microbiota accessible carbohydrates or fermentable dietary fibre, the reverse is not true. The prebiotic concept is an area of current debate[70]
- Synbiotics contain a mixture of prebiotics and probiotics

Table 2 | Summary of systematic reviews analysing the role of probiotics on clinical outcomes

Outcome	Reference	No of studies/ participants	Evidence of benefit?	Results/conclusions
Clostridium difficile associated diarrhoea in adults and children	Goldenberg et al (2017)[111]	39/9955	Yes	Moderate quality evidence that probiotics are safe and effective for preventing *C difficile* associated diarrhoea. (RR 0.30, 95% CI 0.21 to 0.42)
Necrotising enterocolitis	Al Faleh et al (2014)[112] Rees et al (2017)[113]	17/5338	Yes	Enteral supplementation of probiotics prevents severe necrotising enterocolitis (RR 0.43, 95%CI 0.33 to 0.56) and all cause mortality in preterm infants (RR 0.65, 95% CI 0.25 to 0.81)
Antibiotic associated diarrhoea in children	Goldenberg et al (2015)[114]	26/3898	Yes	Moderate evidence of a fall in the incidence of antibiotic associated diarrhoea in the probiotic *v* control group (RR 0.46, 95% CI 0.35 to 0.61; I^2=55%, 3898 participants)
Probiotics for preventing acute upper respiratory tract infections	Hao et al (2015)[115]	12/3720	Yes	Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute upper respiratory tract infections, the mean duration of an episode, antibiotic use, and related school absence (12 trials, 3720 participants including children, adults, and older people)
Urinary tract infections	Schwenger et al (2015)[116]	9/735	No	No significant benefit for probiotics compared with placebo or no treatment
Prevention of asthma and wheeze in infants	Azad et al (2013)[117]	6/1364	No	No evidence to support a protective association between perinatal use of probiotics and doctor diagnosed asthma or childhood wheeze
Prevention of eczema in infants and children	Mansfield et al (2014)	16/2797	Yes	Probiotic supplementation in the first several years of life did have a significant impact on development of eczema (RR 0.74, 95% CI 0.67 to 0.82)
Prevention of invasive fungal infections in preterm neonates	Agrawal et al (2015)[119]	19/4912	Unclear	Probiotic supplementation reduced the risk of invasive fungal infections (RR 0.50, 95% CI 0.34 to 0.73, I^2=39%) but there was high heterogeneity between studies. Analysis after excluding the study with a high baseline incidence (75%) showed that probiotic supplementation had no significant benefits (RR 0.89, 95% CI 0.44 to 1.78)
Prevention of nosocomial infections	Manzanares et al (2015)[120]	30/2972	Yes	Probiotics were associated with a significant reduction in infections (RR 0.80, 95%CI 0.68 to 0.95, P=0.009; I^2=36%, P=0.09). A significant reduction in the incidence of ventilator associated pneumonia was found (RR 0.74, 95% CI 0.61 to 0.90, P=0.002; I^2=19%)
Treatment of rotavirus diarrhoea in infants and children	Ahmadi et al (2015)[121]	14/1149	Yes	Probiotic supplementation resulted in a mean difference of −0.41 (CI 95% −0.56 to −0.25; P<0.001) in the duration of diarrhoea. Probiotics exert positive effect on reducing the duration of acute rotavirus diarrhoea compared with control
Prevention and treatment of Crohn's disease and ulcerative colitis	Saez Lara et al (2015)[122]	14/821 ulcerative colitis 8/374 Crohn's disease	Yes	The use of probiotics and/or synbiotics has positive effects in the treatment and maintenance of ulcerative colitis, whereas in Crohn's disease clear effectiveness has only been shown for synbiotics (no meta-analysis was performed)
Pulmonary exacerbations in children with cystic fibrosis	Ananathan et al (2016)[123]	9/275	Yes	Significant reduction in the rate of pulmonary exacerbation (two parallel group randomised controlled trials and one crossover trial: RR 0.25, 95% CI 0.15 to 0.41; P< 0.00001)
Type 2 diabetes (fasting glucose, glycated haemoglobin test)	Akbari et al (2016)[124]	13/805	Yes	Probiotics significantly reduced fasting blood glucose compared with placebo (8 studies; standardised mean difference −1.583; 95% CI −4.18 to 4.18; P=0.000). Significant reduction in HbA_{1c} was also seen (6 studies; SMD −1.779; 95% CI, −2.657 to −0.901; P=0.000)
Type 2 diabetes (insulin resistance, insulin levels)	Zhang et al (2016)[125]	7/425	Yes	Probiotic therapy significantly decreased homeostasis model assessment of insulin resistance (HOMA-IR) and insulin concentration (WMD: −1.08, 95% CI −1.88 to −0.28; and weighted mean difference −1.35mIU/L, 95% CI −−2.38 to −0.31, respectively
Necrotising enterocolitis in pre-term neonates with focus *on Lactobacillus reuteri*	Athalye-Jape et al (2016)[126]	6/1778	Yes	Probiotic reduced duration of hospitalisation (mean difference = −10.77 days, 95% CI −13.67 to −7.86; in 3 randomised controlled trials), and late onset sepsis (RR 0.66; 95% CI, 0.52 to 0.83; 4 RCTs) were reduced in the
Reduction of serum concentration of C reactive protein	Mazidi et al (2017)[127]	19/935	Yes	Significant reduction in serum C reactive protein after probiotic administration with a WMD −1.35 mg/L, (95% CI −2.15 to −0.55, I^2 65.1%)
Cardiovascular risk factors in patients with type 2 diabetes	Hendijani et al (2017)[128]	11/641	Yes	Probiotic consumption significantly decreased systolic blood pressure (−3.28 mm Hg; 95% CI −5.38 to −1.18), diastolic (WMD −2.13 mm Hg; 95% CI −4.5 to 0.24), low density lipoprotein cholesterol (WMD 8.32 mg/dL; 95% CI −15.24 to −1.4), total cholesterol (WMD −12.19 mg/dL; 95% CI −17.62 to −6.75) and triglycerides(WMD −24.48 mg/dL; 95% CI −33.77 to −11.18) compared with placebo
Reduction of total cholesterol and low density lipoprotein cholesterol	Wu et al (2017)[129]	15/976	Yes	*Lactobacillus* consumption significantly reduced total cholesterol by 0.26 mmol/L (95% CI −0.40 to −0.12) and LDL-C by 0.23 mmol/L (95% CI, −0.36 to −0.10)
Depressive symptoms	Wallace and Milev (2017)[79,130]	6/1080	Yes	No quantitative analysis was performed. Most studies found positive results, and the authors conclude that compelling evidence shows that probiotics alleviate depressive symptoms
Vulvovaginal candidiasis in non-pregnant women	Xie et al (2018)[131]	10/1656	Yes	Probiotics increased the rate of short term clinical cure (RR 1.14, 95% CI 1.05 to 1.24, low quality evidence) and mycological cure (RR 1.06, 95% CI 1.02 to 1.10, low quality evidence) and decreased relapse rate at one month (RR 0.34, 95% CI 0.17 to 0.68, low quality evidence)
Chronic periodontitis	Ikram et al (2018)[132]	7/220	Yes	The overall mean difference for gaining clinical attachment level gain between probiotics and placebo was significant (weighted mean difference 1.41, 95% CI 0.15 to 2.67, P=0.028)

RR=risk ratio, SBP systolic blood pressure, DBP= diastolic blood pressure, TC= total cholesterol, TG= serum triglycerides, SMD=standardised mean difference, WMD=weighted mean difference' CI=confidence interval

profiles of the candidate microbes in inflammation, cancer, lipid metabolism, or obesity.[92] Stable engraftment of a probiotic *Bifidobacterium longum*, for example, has been shown to depend on individualised features of the gut microbiota, providing a rationale for the personalisation of probiotic applications.[93]

Personalised nutrition and future directions

Given the variation in the gut microbiota between people, the optimal diet of a person may need to be tailored to their gut microbiota. Zeevi et al.[94] obtained a multi-dimensional microbiota profile in 900 people and monitored food intake, continuous blood glucose levels, and physical activity for one week. The researchers devised a machine learning algorithm to predict personalised glucose responses after meals based on clinical and gut microbiome data and showed that it achieved significantly higher predictions than approaches such as carbohydrate counting or glycaemic index scores. In a follow-up double blinded randomised crossover trial of 26 participants, personalised dietary interventions based on the algorithm successfully normalised blood glucose levels.[94]

A study on response to bread[68] using a randomised crossover trial of one week long dietary interventions showed significant interpersonal variability in the glycaemic response to different bread types. The type of bread that induced the lower glycaemic response in each person could be predicted based solely on microbiome data collected before the intervention.[68] Much more research is needed to establish whether these kinds of personalised approaches are feasible, sustainable, and have a positive effect on clinical outcomes.

Conclusions

We are entering an era where we can increasingly modify health through food and measure the effects through our microbes or metabolites. Fibre is a key nutrient for a healthy microbiome and has been overlooked while debates have raged about sugar and fat. The adverse effects on the microbiome of drugs and processed food ingredients can no longer be ignored. Given the current gaps in knowledge, we need clinical evidence that can be translated into clinical practice, ideally through randomised controlled studies that use consistent matrices of prebiotics or probiotics or faecal microbiota transplantation to assess changes in gut microbiota composition and in health outcomes.

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