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Review article: dietary fibre in the era of microbiome science

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Summary

Background: Explanations for the health benefits of dietary fibre have, in the past, been inconsistent and studies of the physiological effects of dietary fibre were, perhaps, directed at the wrong read-outs. Confounding factors included a failure to appreciate the molecular diversity and varied properties of fibre-types and the role of fibre as a substrate for microbial metabolism in the gut.

Aim: To present a modern perspective on fibre science and to encourage clinicians to re-consider the health impact of dietary fibre and how best to approach adjustments in dietary consumption.

Methods: This perspective is drawn selectively from recent microbiome science; no attempt was made to perform an exhaustive review of all articles related to every aspect of dietary fibre.

Results: Advances in microbiome science have revealed not only the functional impact of dietary fibre on the composition and function of the microbiota but have also demonstrated the physiologic responses to microbial-derived metabolites from fibre digestion. Moreover, studies have shown the personalised nature of host responses to dietary fibre intervention, with outcomes being dependent on individual pre-treatment gut ecology.

Conclusions: The physical properties of dietary fibres are important for homeostasis within the gut, but the predominant health benefits extend beyond the gut to enhanced metabolic welfare, including protection against obesity and related metabolic diseases. Fibre is a form of functional food joining a growing list of examples of diet-microbe-host interactions which link microbe-host metabolic and immune cascades.

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1 | INTRODUCTION

Once was a time when gastroenterologists regarded (or disregarded) dietary fibre as the undigested component of natural foods which gave the colon a good work-out. Fibre was seen to add bulk to stools and to promote orderly bowel function, by which regular bowel habits was intended and was in some vague way good for health in general and for "functional" bowel disorders, in particular. Those who were privileged to hear the iconic Denis Burkitt were struck by the Irishman's persuasive rhetoric, refreshing in its directness and simplicity: "if you pass small stools (low dietary fibre) you have to have large hospitals."[1] Then followed a period of disappointment, when dietary fibre seemed to be unhelpful in irritable bowel syndrome[2] and other presumed clinical benefits could not be demonstrated. As these cold facts emerged, Burkitt's stock was in decline and viewed, by some, as "hot air".[3] Sadly, few gastroenterologists considered the details behind dietary fibre science. What is the appropriate dose of fibre for a healthy diet? Is there a difference between soluble and insoluble fibre? What is fibre and what happens to it in the human gut? Today, Burkitt's star is rising again and fibre science is undergoing a remarkable phase of revisionism in light of developments in microbiome science. With the expanding knowledge of diet- microbe- host interactions, clinicians once again have to consider the health impact of dietary fibre and how best to advise regarding adjustment of dietary consumption.

2 | DEFINING DIETARY FIBRE

Fibre is not a single substance but rather a heterogeneous group of materials, each with different biologic effects. It is comprised of plant-derived carbohydrate which evades typical human amylase-driven digestion in the absence of cellulase availability required for its breakdown. Instead, consumption by humans requires digestion by microbes, using anaerobic fermentation, the end products of which are short chain fatty acids (SCFA). Consequently, terms such as microbiota accessible carbohydrates (MACs) to describe fibre have emerged.[4,5] While the fermentation process separates most forms of dietary fibre from digestible carbohydrates, such as sugar and starch,[6] the distinction requires a more comprehensive definition. In addition, the fibre analysis methods of the Association of Official Analytical Chemists (AOAC) and those of Englyst lead to variability in measuring fibre content of food which impacts both recommended intake and standardised definitions.[7]

Definitions of dietary fibre have been offered by The Codex Alimentarius Alinorm, an internationally recognised food standards programme (a joint commission by the Food and Agriculture Organization of the United States [FAO] and the World Health Organization [WHO]), with apparent acceptance.[8–10] Dietary fibre may be defined as polymers with 10 or more monomeric units which are neither digested nor absorbed in the human intestine. The decision whether to include monomeric unit counts of 3-9 is left to national authorities.[8,10] In Europe, a minimum count of 3 is accepted and includes resistant (nondigestible) oligosaccharides (monomeric unit 3-9), nonstarch polysaccharides (monomeric unit ≥10) and resistant starch (monomeric unit ≥10)[8] (Figure 1). Lignin and other compounds associated with polysaccharides in plant cell walls are included in the definition as long as they remain associated with the oligosaccharide or polysaccharide fraction.[8,9]

Dietary fibre may be subtyped by properties of solubility, viscosity and fermentation and, although there is significant overlap, this is of practical use to correlate certain dietary fibre characteristics to observed health outcomes (Figure 2).[2,11,12] Solubility refers to dissolution in water, but it is the viscosity (capacity to gel with water) of certain soluble fibres that influences chyme consistency and slows digestion of consumed nutrients to absorbable components by digestive enzymes.[13–18]

Oligosaccharides are highly soluble and fermentable fibres and include fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS). These short chain fibres are highly fermentable due to their small size and solubility.[6] The remaining subtypes, polysaccharides and resistant starch are broadly categorised as long chain fibres according to their properties (Figures 1 and 2).

Soluble, nonviscous, readily fermentable fibres (inulin, wheat dextrin) dissolve in water and are rapidly and completely fermented. Soluble, viscous, readily fermentable fibres (β-glucan, gums, pectin) are similar but form a gel-like consistency with water. These characteristics are then lost following fermentation.[10,13–17] Soluble, viscous, slowly fermented fibres (psyllium) also form a gel-like consistency, but do not undergo extensive fermentation.[13] As such, the capacity to interact with water is preserved throughout the colon. This allows softening of stools in those suffering from constipation and adds form to loose stools.[13,16,17]

Insoluble fibres (wheat bran, lignin, cellulose) exert a laxative effect by stimulation and irritation of gut mucosa to increase secretion and peristalsis. Large and coarse dietary fibre particles have a greater effect on stool bulking and transit time.[16,19–21]

3 | BIOLOGIC EFFECTS OF DIETARY FIBRE AND END PRODUCTS OF FIBRE METABOLISM

The action of fibre depends on solubility, viscosity and fermentation. Viscosity influences chyme consistency, digestion, absorption and satiety.[22,23] These effects are associated with reduced intake and offer therapeutic value in the management of obesity and related complications including the metabolic syndrome.[23] Viscous fibres, such as psyllium, delay degradation and absorption of nutrients can reduce total glucose and cholesterol absorption by up to 12%.[24,25] Nutrients then reach the distal small bowel, where the mucosal response includes release of glucagon-like peptide-1 (GLP-1). The result is decreased appetite, decreased glucagon secretion, improved insulin sensitivity and delayed gastric emptying (the "ileal brake" phenomenon),[13] thereby improving glycaemic control. In addition, fibre

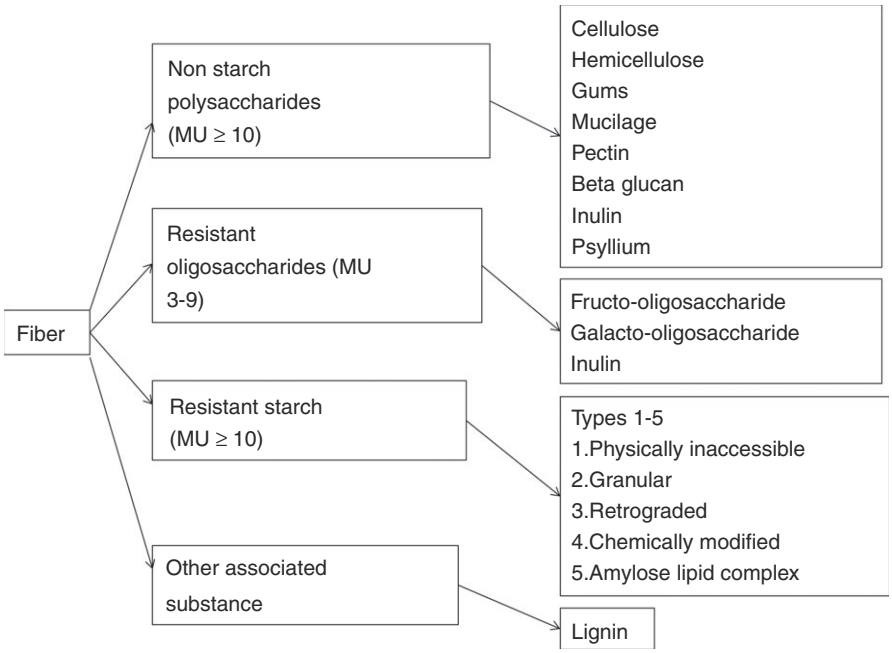

FIGURE 1 Fibre subtypes by polymer length. This is not exhaustive list of fibre examples

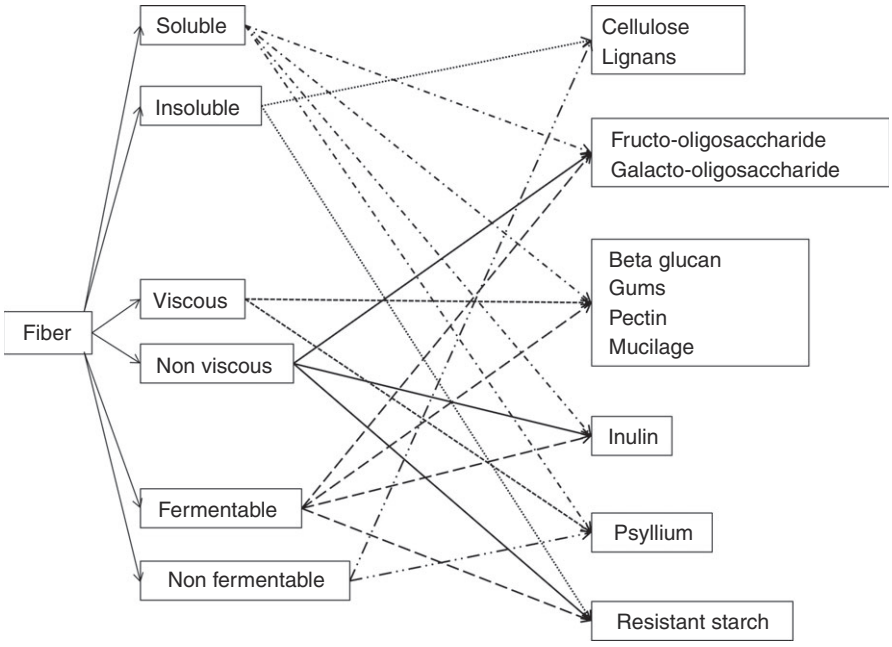

FIGURE 2 Overlapping properties of fibre by solubility, viscosity and fermentation

plays a role in nutrient bioavailability as it binds ions such as copper, calcium and zinc, which are released in the distal gut as fibre is fermented, where these ions exert effects such as local anti-microbial action.[10]

Fermentation of fibre by gut microbiota yields SCFAs that provide energy for the host, but also exert an immunoregulatory and gut-brain signalling role (Figure 3).[26–31] The primary SCFAs produced from fibre fermentation are acetate (C2), propionate (C3) and butyrate (C4).[27–32] Acetate is produced from pyruvate via acetyl-CoA or via the Wood-Ljungdahl pathway. Propionate is produced from succinate conversion to methylmalonyl-CoA via the succinate pathway and is also synthesised from acrylate, with lactate as a precursor, through the acrylate pathway or the propanediol pathway. Butyrate is formed first by condensation of two molecules of acetyl-CoA and reduction to butyryl-CoA, which can be converted to butyrate either by the butyryl-CoA: acetate CoA-transferase route or via butyrate kinase and phosphotransbutyrylase.[33,34] Acetate is the most abundant SCFA detectable in human peripheral circulation, as propionate is metabolised by the liver and butyrate is the primary source of energy used by colonocytes.[33]

Butyrate and, to a lesser extent, propionate are known to act as histone deacetylases (HDAC) inhibitors. Histone acetylation increases

accessibility of the transcriptional machinery to promote gene transcription; acetyl groups are added to histone tails by histone acetyltransferases (HATs) and are removed by HDAC. HDAC inhibition exerts anti-inflammatory and immune effects through suppression of pro-inflammatory macrophage responses and differentiation of dendritic cells from bone marrow stem cells as well as regulating cytokine expression in T cells and generation of regulatory T cells (Tregs).[33]

Further immune effects occur via G-protein coupled receptor (GPCR) signalling. Butyrate-stimulated signalling of GPR109A and GPR43 (GPCRs) increases generation of Tregs, interleukin (IL)-10-producing T cells and IL-18 secretion by intestinal epithelial cells,[35] while also activating NLRP3 inflammasome, which is critical for intestinal homeostasis.[33,36] This attenuates the inflammatory response, through release of IL-18, of the mucosal immune system to gut commensal microbes and promotes gut barrier integrity.[33,37] Fibre-rich diets, in animal studies, are also associated with increased mucosal thickness and reduced permeability in the gut, which improves mucus layer function and reduces bacterial translocation and infection.[38–40]

GPR41 and GPR43 appear to have important roles in metabolic homeostasis as well as immune function. Acetate and propionate are potent activators of these GPCRs.[33] GPR43 promotes GLP-1 secretion in the intestine, as well as regulating energy uptake in white adipose tissue (WAT) outside the gut.[33,41] In animal models, GPR43 over-expression is associated with leaner mice,[41] whereas GPR41 is associated with microbial- induced adiposity.[33] GPR41$^{-/-}$ knock-out mice are leaner than wild-type counterparts, though this association does not occur under germ-free conditions.[42] Peptide YY production via microbial and SCFA signalling also occurs in a GPR41 dependent fashion and has a role in delaying gut motility and prolonging nutrient absorptive capacity.[42] Further metabolic functions include

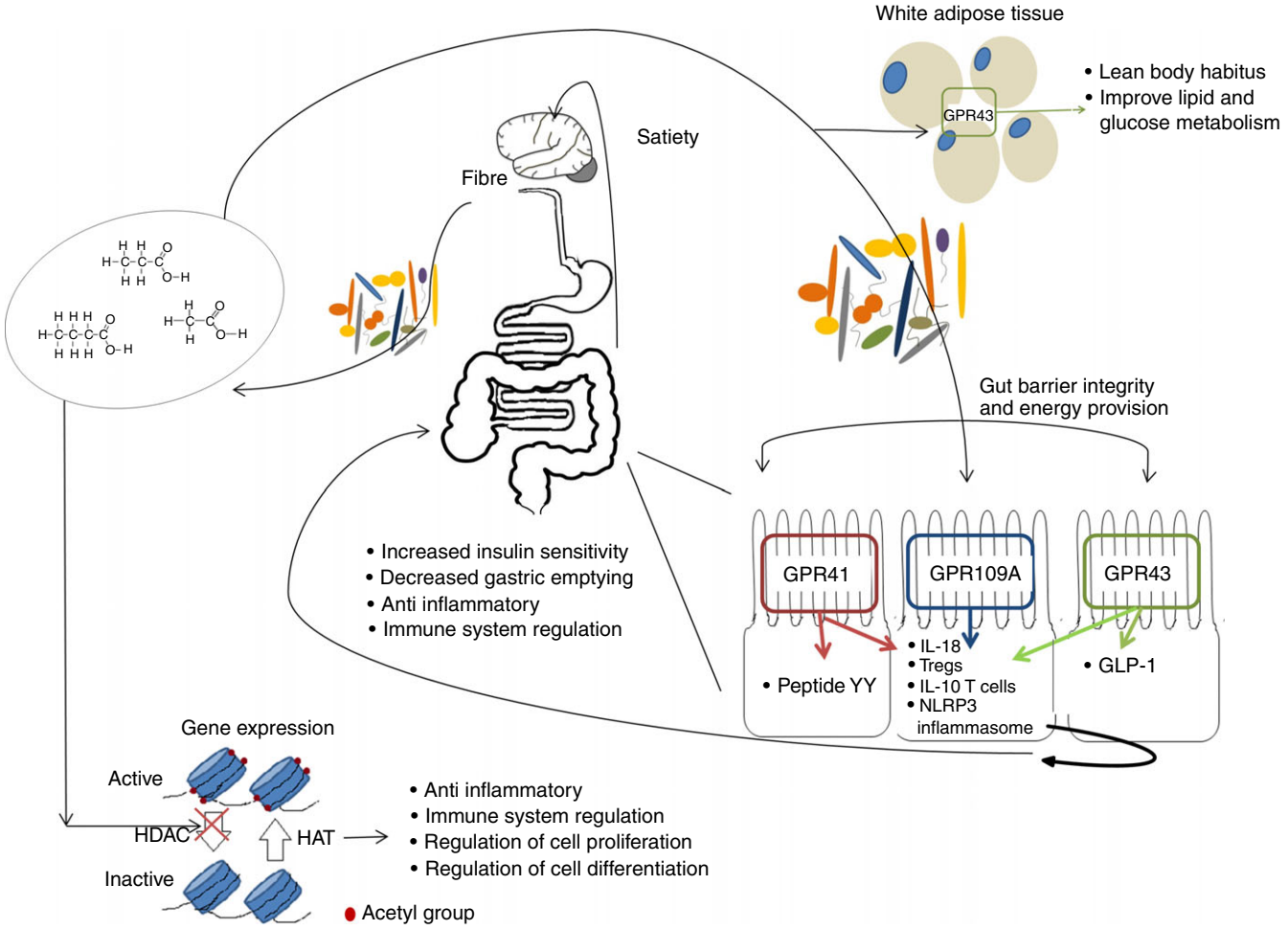

FIGURE 3 Complexity of diet-microbe-host interaction illustrated with example of short chain fatty acids (SCFAs). Microbial fermentation of fibre produces SCFAs; acetate, propionate and butyrate, which have influences on microbial, metabolic and immune homeostasis. Butyrate and propionate inhibit histone deacetylases (HDAC) to allow ongoing chromatin gene expression via acetylation with anti-inflammatory and immune effects. SCFAs activate GP109A, GPR41 and GPR43 (GPCR) with immune system influences including increased IL-18, regulatory T cells (Tregs), IL-10 producing T cells and activation of the NLRP3 inflammasome. Lipid and glucose metabolism is altered through GPCR mediated hormone activation including peptide YY and GLP-1 as well as GPR41/43 receptors on white adipose tissue (WAT). SCFA, Short chain fatty acid; GPCR, G-protein coupled receptors; IL-18, interleukin-18; IL-10, interleukin-10; Peptide YY, peptide tyrosine; GLP-1, glucagon like peptide-1; HAT, histone acetyltransferase; HDAC, histone deacetylase

increased insulin sensitivity and glucose tolerance via gut-brain neural signalling, induced by propionate and butyrate mediated de-novo glucose synthesis in gut epithelium.[33] Thus, SCFA signalling of GPCRs, in animal models, appears to have clear metabolic influences and specific effects in humans are worth exploring.[33]

Potentially substantial end points in fibre metabolism and fermentation in humans due to described SCFA-induced immunoregulatory and anti-inflammatory influences may offer new targets in fibre-related health outcomes. This is in addition to the metabolic benefits of various soluble and viscous fibres. Current described biological effects of individual fibre components and sources of these fibres, are summarised in Table 1.

4 | VARIABILITY OF RESPONSE TO DIETARY FIBRE

As fibre is digested by microbes, a beneficial response to dietary fibre intervention may be dependent on the established microbiota. Diet influences which microbes colonise, flourish, retain or disappear in humans throughout life.[10,26] Long-term dietary habits with little dietary fibre intake results in diminished microbial diversity.[26,43,44] The response to increased dietary fibre intake is, therefore, not uniform and varies depending on the composition of an individual's pre-existing microbiota which is influenced by previous dietary habits.[26,43–52] Dietary and lifestyle habits of rural African children is associated with a microbiome enriched with Bacteroidetes and reduced Firmicutes phyla when compared with microbiota of European children.[53] Of the Bacteroidetes, a Prevotella-enriched microbiome is associated with higher concentrations of SCFAs due to specific enzymes for polysaccharide breakdown.[54] Furthermore, healthy subjects with improved glucose metabolism following fibre supplementation had a higher Prevotella/Bacteroides ratio than those who did not respond to increased fibre.[55]

Low-fibre diet fed to ex-germ-free mice containing a human faecal microbiome leads to progressive loss of microbial diversity, which is only partially reversible on fibre re-introduction. If this reduced microbial diversity with missing taxa is transmitted to subsequent generations, fibre re-introduction is unable to reverse these losses[56] (Figure 4). This may be of particular significance when considering dietary advice for antenatal women and to establish microbial diversity in the neonate. Further murine studies suggest impaired microbial responses to dietary intervention, reflective of previous dietary habits, may necessitate introduction of specific dietary-responsive bacteria from other individuals.[57] In pig microbiome analysis, high fibre/low-fat diet is associated with higher concentration of Bifidobacteria, Lactobacilli and *Faecalibacterium prausnitzii*, which have a protective role in intestinal inflammation,[58] as well as increased SCFA production.[59] In the same study, high fat/low fibre diet led to increased abundance of Enterobacteriaceae, which in humans has been associated with overweight and type 2 diabetes and includes the pathogenic strains *Escherichia coli* and *Salmonella enterica*.[59] Further evidence favouring a fibre-based diet is provided by a murine model of antibiotic-induced *Clostridium difficile* infection (CDI).[5] In this study, a diet deficient in fibre was linked with prolonged CDI, while addition of either inulin or a fibre mixture reduced the burden

TABLE 1 Fibre subtypes[8,13,14,18]

Fibre subtype	Structure	Source	Metabolic effect
Cellulose	Linear chains of glucose units with beta-1, 4 glucosidic linkage	Cereals, legumes, nuts	Increases stool bulk and stimulates peristalsis
Hemicellulose	As cellulose with xylose, galactose, mannose and arabinose sugar branches	Cereals, cell walls of fruits, vegetables	Varies with source; mix of insoluble, soluble and viscous properties
Lignan	Complex polymer of aromatic alcohols. Not a polysaccharide	Cereals, plant cell walls	Increases stool bulk and stimulates peristalsis
Gums	Mannose backbone with galactose side chains	Legumes, nuts	Cholesterol and glucose lowering effects, slow digestion and absorption, Fermentation by microbiota
Pectin	Polygalacturonic acid, D-galacturonic acid unit backbone, substituted with arabinans, galactin, arabinogalactin side chains	Fruit peel, legumes, beetroot	Cholesterol and glucose lowering effects, Slow digestion and absorption, Fermentation by microbiota
Beta glucan	Beta-D glucose linear backbone with 1-3 beta glycosidic linkage	Cereals and grains, yeasts, fungi and bacteria	Cholesterol and glucose lowering effects, Fermentation by microbiota
Inulin	Beta 1-2-fructan residue backbone, often glucosyl units as chain terminating moieties	Chicory root, onion, cereals	Lower triglyceride concentration, Fermentation by microbiota
Psyllium	Heteroxylan with 1:4, 1:3 linkage backbone, side chains of arabinose, xylose, galactose and rhamnose	*Plantago Ovata*	Cholesterol and glucose lowering, Stool forming effects
Oligosaccharides	Beta- fructo- oligosaccharides (FOS) Alpha and beta-galactooligosaccharides (GOS)	Polymers derived from polysaccharides by hydrolysis	Fermentation by microbiota
Resistant starch (RS1-5)	Alpha-1,4-D-glucan links	Cereals, legumes, fruits	Cholesterol and glucose lowering, Fermentation by microbiota

of *C difficile* and supported a microbial diversity favouring exclusion of *C difficile*.[5]

The impact of diet also appears to be reflected in various human studies. Fibre supplementation in Canadian children resulted in significant increases in *Bifidobacterium* genus and a decrease in *Bacteroides vulgatus*, which correlated with reduced adiposity.[60] The microbiome of children from the West African country of Burkina Faso, with a fibre-rich African diet, has been compared with that of children in Italy. The microbiota of the African children had significantly higher proportions of Prevotella, Xylanibacter, Butyrivibrio and Treponema genera. These are known to contain genes for cellulose and xylan hydrolysis to maximise fermentation of dietary fibre.[53] The Hadza tribe of Tanzania, a hunter-gatherer community, have a more diverse faecal microbiome that is linked to their foraging lifestyle, compared with industrialised countries.[61] The Hadza dietary habits are similar to those of human ancestors and interestingly, their microbiome contains unclassified Bacteroidetes and Clostridiales, broadening their diversity more than their established fibre enrichment of Prevotella, Treponema and Clostridiales.[61] Compared with Italian adult microbiota, the Hadza microbiota has a higher abundance of Bacteroidetes, in particular Prevotella and less Firmicutes, consistent with how high dietary fibre intake influences the composition of the microbiome. A recent systematic review further concluded that, in healthy adults, fibre intervention, particularly with fructans and galacto-oligosaccharide, leads to increased abundance of both *Bifidobacterium* and *Lactobacillus* species.[62]

In contrast, elderly western populations have reduced gut microbial diversity which correlates significantly with nutritional status, frailty, co-morbidity, markers of inflammation and faecal water metabolites. Furthermore, a significantly less diverse microbiota is found amongst elderly subjects in long-term care facilities versus those in the community, with a less diverse diet of those in long-term care facilities at least partly implicated in the microbial species collapse.[63] It is evident that a fibre-based diet, in both animal and human studies, has favourable effects on gut microbial diversity which, in turn, influences the fermentation by-products of fibre metabolism. It remains to be determined if fibre alone is sufficient to reverse microbial collapse in humans, though current evidence would suggest that a re-introduction of specific fibre-sensitive taxa may be required in addition to high fibre diet.

5 | RE-INTRODUCING FIBRE TO THE WESTERN DIET

The Academy of Nutrition and Dietetics recommend that fibre is consumed in adequate amounts as part of a balanced diet. What does this actually mean? Reference intakes suggest 14 g of dietary fibre per 1000 kcal consumed, which equates to 25 g for females and 38 g for males, depending on energy intake.[64,65] The National Academy of Sciences Institute of Medicine similarly recommend 20-35 g/d[6] and the Scientific Advisory Committee on Nutrition (SACN) recommend 30 g/d.[66] Despite this, current dietary fibre consumption in socioeconomically developed societies, such as the United States of America, is estimated at only 12-18 g/d.[64,67,68] Figures in Europe vary but remain highest in Italy and lowest in Sweden and the UK general population.[69] In Africa, among rural South African and Ugandan populations, fibre is consumed in amounts greater than 50 g/d, which is associated with a reduced prevalence of chronic inflammatory disorders.[10,70] Contemporary consumption of dietary fibre remains far less than that exhibited by ancestral humans who had estimated intakes of up to 100 g/d.[71] The striking reduction in fibre consumption is partly attributable to changes in agricultural practices and production of fibre-based foods.[71] Reliance on energy dense, high glycaemic-load convenience foods is common in western society, largely replacing fibre and so recommended dietary fibre intakes are now seldom achieved.[65,72,73] Restoration of fibre after a prolonged period of dietary deficiency represents a significant challenge, not simply educational but also physiological.

Abrupt addition of or change in fibre intake leads to bloating, abdominal cramps and increased flatulence.[6,74] Furthermore, delayed

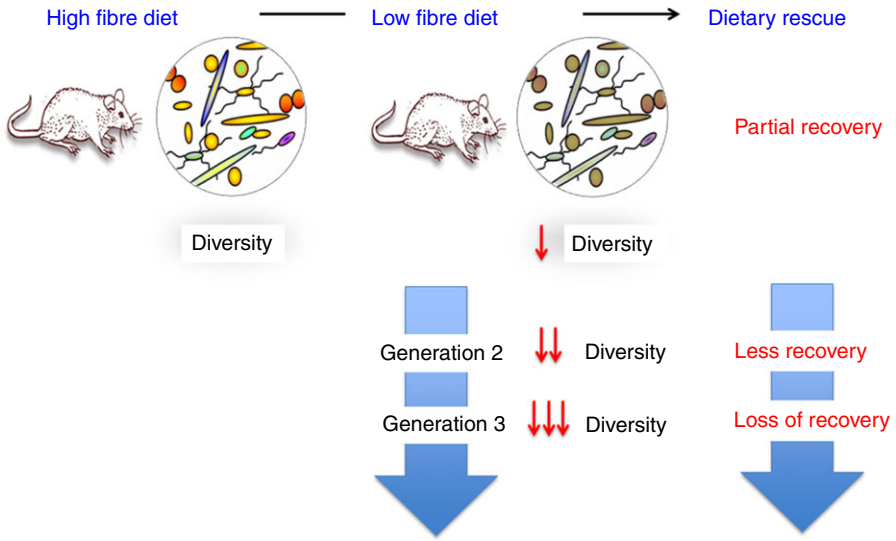

FIGURE 4 Irreversible loss of microbial species with dietary fibre restriction over time and down the generations in experimental animals harbouring a human microbiome. Based on Sonnenburg et al. *Nature* 2016[56]

gastric emptying and digestion, from soluble and viscous fibres, may aggravate symptoms of dyspepsia. This was identified in a small study where transient lower oesophageal sphincter relaxations were observed with fibre supplementation.[75] These unwanted symptoms are associated with many gastrointestinal and functional disorders and when coupled with negative social connotations of increased gas and flatulence may affect adherence. Clinical practice favours slow titration of fibre to achieve daily fibre intake in accordance with guideline recommendations.[6,64–66] Dietary fibre advice should not be glib and needs attention to detail for dose titration to avoid or reduce gas production and cramps, together with education on the expected benefits of fibre. Fibre intake guidelines as initial targets in clinical studies may allow future increases in doses that may even approach ancestral intake in appropriates individuals.

6 | WHO NEEDS DIETARY FIBRE?

Optimal fibre intake is a consideration for all. Fibre is no longer a nutrient primarily recommended by the gastroenterologist, but for all clinicians when considering dietary advice for patients. Modern criteria for assessing the effects of dietary fibre include metabolic parameters, microbiome composition and metabolite production. The rising prevalence of metabolic syndrome is relevant to all medical specialities and fibre is a readily available and inexpensive strategy for favourably influencing cholesterol and glucose metabolism, while increasing satiety and modifying immune system function. A recent meta-analysis reported an inverse association between dietary fibre intake and risk of metabolic syndrome.[76] Despite the identification of a range of mechanisms responsible for this relationship, further prospective cohort studies are required. Additionally, fibre is required to maintain gut microbial diversity and, potentially in antenatal care, to prevent loss of taxa for subsequent generations.[56] Reduced microbial diversity, as a consequence of Western lifestyle and diet, has been linked to co-morbidity and inflammation and suggests a potential role for fibre in disease prevention by maintaining microbial diversity.[63,67] The use of a fibre-based diet to reduce infective risk of *C difficile* may be one such example.[5] As microbial response is dependent on individual baseline microbiota composition, dietary fibre adjustments based on microbiome readouts will enable a more scientific approach to achieving full benefits of fibre and SCFA production.

7 | CHALLENGES AND DISAPPOINTMENTS

In the past, several factors undermined enthusiasm for the health benefits of fibre. First was the undue emphasis on gastrointestinal pathology rather than metabolic disease. Second, some challenged Burkitt's enthusiasm for fibre by pointing to confounding variables such as healthy lifestyle factors including reduced smoking, greater exercise and consumption of nonfibre nutrients found in fruit and vegetables.[3] Third, there were exaggerated expectations for the therapeutic potential of fibre in reversing gastrointestinal pathology.[3,77,78] The potential for fibre to prevent rather than treat infectious, diverticular and neoplastic disorders would have been a more realistic objective. Changes in the microbiota in the peri-diverticular region may be an important step in diverticular disease pathogenesis and inflammation and a more appropriate target for fibre intervention.[79]

Inconsistent and confusing results from trials investigating dietary fibre and colorectal cancer risk led some to further question Burkitt's early claims.[3,80–82] However, much of the available prospective data have demonstrated an inverse relationship between fibre intake and incident colorectal cancer risk.[80,83–86] The previous discrepancies are likely explained by a lack of evidence for fibre in reducing the risk of recurrent adenomatous colorectal polyps.[78,86,87] Proposed mechanisms for a protective fibre effect on colorectal cancer risk include dilution of faecal carcinogens, quicker gut transit times, SCFA production and binding of carcinogenic bile acids.[80,81] In addition, butyrate can improve colonic atrophy by providing an energy source and as the primary source of energy for cancer cells is glucose, butyrate does not influence cancer cell proliferation.[33] Furthermore, the expression of GPR109A and GPR43 receptors is markedly reduced in colon cancer, suggesting a protective role of SCFA signalling.[33]

8 | CONCLUSIONS

Difficulties in defining dietary fibre have led to difficulty defining its health role. The type of fibre, titration of dose, solubility, viscosity and fermentation properties all influence the benefits of a specific fibre in humans. Expanding knowledge of fibre- microbe-host interactions and production of SCFAs by fermentation have reaffirmed some of the previous health benefits attributed to fibre. Despite this, fibre intake remains low in Western societies. Given the range of health benefits associated with specific functional dietary fibres, an opportunity exists for the food industry concerning food reformulation and fortification. Re-introduction of fibre should be a gradual continuous process, never a rapid change, due to uncomfortable and socially undesirable, gas production and cramps.

Lessons from the past should be learned; we believe that the most useful end goal assessments of fibre are metabolic parameters and microbial composition rather than unrealistic goals such as cancer and diverticular disease therapy. Microbiome read-outs will help predict those with the greatest likelihood of a beneficial response to dietary fibre and may inform personalised dietary recommendations for consumption of specific fibre types based on microbial composition. Thus, modern microbiome science can complement traditional nutrition and food science to comprehensively reassess Burkitt's claims that the gut, not the heart, is key to health.[46]

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