

This is why gut health is the hottest of hot topics



2796 Cell 184, May 13, 2021 © 2021 Elsevier Inc. DOI https://doi.org/10.1016/j.cell.2021.04.026



legends and references

Jennifer H. Hill and June L. Round Department of Pathology, Division of Microbiology and Immunology, University of Utah School of Medicine, Salt Lake City, UT 84112, USA Colonization resistance Developmental ↑ Microbes promote increase in Beneficial interaction Detrimental interaction modulation of host Local immunomodulatory Intestinal barrier Microbes promote decrease in . Either, depending on host Nervous 🔘 🦫 M Endocrine () Both direct and indirect effects of a variety Beneficial microbes indirectly stimulate Both skin and gut microbiota modulate inflammation, of microbes drive developmental and neurodevelopment and reduce behavioral metabolic host phenotypes. disorders and neuroinflammation. Major mechanisms Diseases Diseases h Inflammation Anxiety and ♠ Neurogenesis, Diabetes (type 1 & 2) ♠ Pathogen Psoriasis, eczema, synaptogenesis and myelination Metabolic syndrome/ 1 Insulin production Autism Melanoma Microglia number Parkinson's Fatty liver and PSC Chronic wound Inflammation Multiple sclerosis infection 1nflammation ₱♠ Fat and cholesterol ♠ Serotonin Cardiovascular ↑ Lipase and bile Systemic dissemination of gut & oral microbes ctly inflame vascular tissues, exacerbated by indirect effects of microbes that promote fat/cholesterol storage (a) (b) (b) (b) Immune Blood cancers ♦ Heart size Microbes play a major role in both local (dis **↑** Trimethylamine Atherosclerosis **↑** Inflammation and function Heart attack Diseases Major mechanisms and stroke ↑ Fat and cholestero Lupus **♣** Inflammation ♠ Toxic metabolites Pathogen resistance Upper GI 🔘 🥙 Overabundance of detrimental microbes with direct effects on host tissues tend to drive Diseases Respiratory 🔘 🛞 🔟 Oral, esophagea ↑ Carcinogenic metabolites Both lung and gut microbiota modulat inflammation, to directly and indirectly ↑ Inflammation influence disease Periodontitis Diseases and gastritis ↑ Epithelial proliferation Allergy/asthma ♠ Mucus production ↑ Injection of toxins COPD and 1nflammation cystic fibrosis ♠ O_o consumption Pneumonia and Lower GI 💮 😸 🥎 🖍 Close proximity to host epithelia results in a Flagellin multitude of direct effects on host physiology. Lung cancer Major mechanisms IBD/colitis ↑ Epithelial proliferation Mucus production Celiac disease and peristalsis Colon, pancreatic Immune cell recruitment and development Hirschsprung's ♠ Carcinogenic metabolites Skeletomuscular () ↑ Injection of toxins Gut microbes have multiple indirect influences on muscle and bone development and local Urinary/reproductive Diseases Major mechanisms Vaginal Lactobacillus spp. play important roles Rheumatoid and in female reproductive health, and gut microbes Muscle atrophy 1 Insulin growth factor Reduced fertility ♠ Pathogen resistance Osteoporosis **♦** Serotonin ↑ Sperm count ♦ Osteoblast function ♦♦ Inflammation See online version for

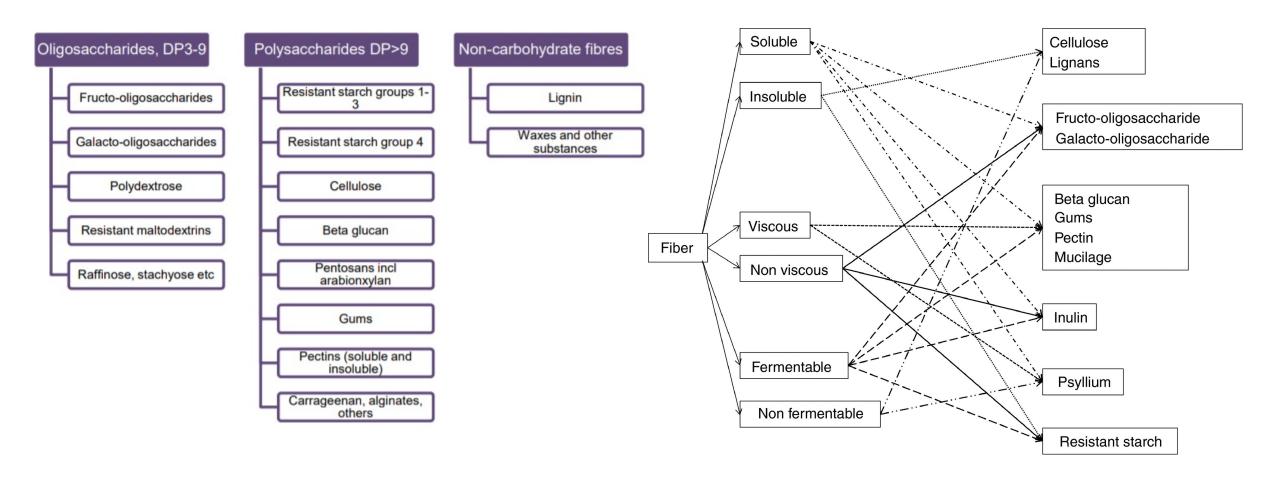
What is fibre?

The fraction of the edible part of plants or their extracts (or synthetic analogues) that are resistant to digestion and absorption in the small intestine, usually with complete or partial fermentation in the large intestine

Promotes one or more of the following beneficial physiological effects:

- Laxation
- Reduction in blood cholesterol
- Modulation of blood glucose

Includes oligosaccharides, polysaccharides and lignins



Westenbrink S et al. *Food Chem* 2013;140:562-7 O'Grady J et al. *Aliment Pharmacol Ther* 2019;49:505-15

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		

The health benefits

Health Benefit
Improved insulin sensitivity (mainly insoluble fibres), reduced risk of developing T2D (mainly insoluble cereal fibres and whole grains) Improved glycaemic status and lipid profiles (mainly soluble fibres), reduced body weight and abdominal adiposity
Gut microbial viability and diversity, metabolites from gut microflora (including SCFAs)
Chronic inflammation, cardiovascular risk, mortality
Chronic inflammation, gut microbiota
Colonic health and integrity, colonic motility, colorectal carcinoma
t Chain Fatty Acids; T2D = Type 2 Diabetes Mellitus.

Prebiotic fibre is like fertiliser for your gut microbiota

And what defines prebiotic fibre continues to broaden as too the health links being made



Today's definition of a prebiotic

Open Access | Published: 14 June 2017

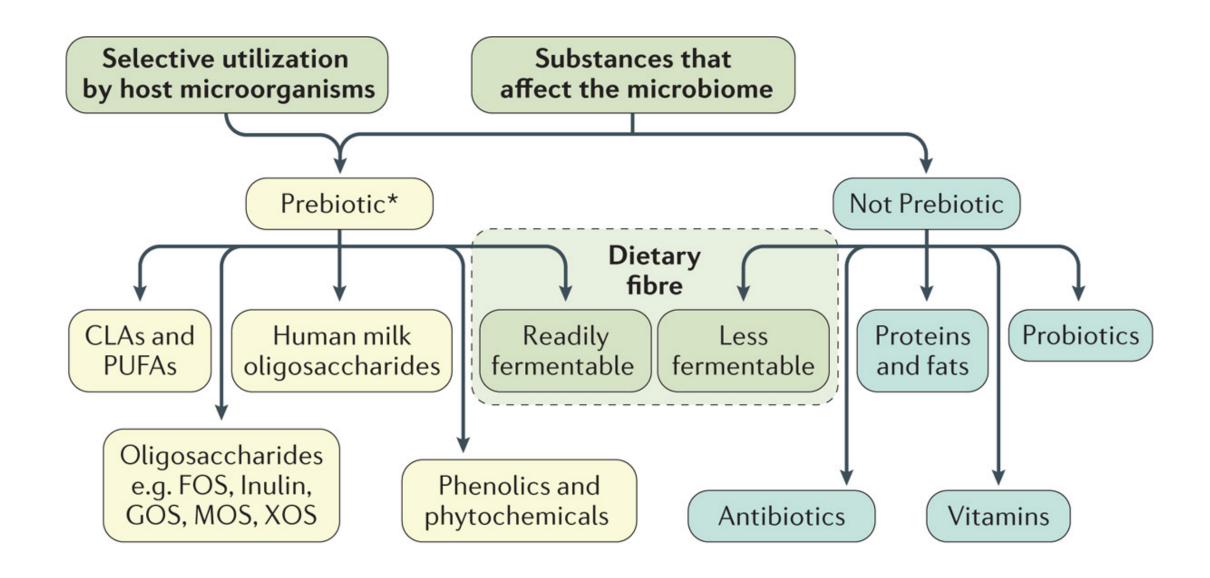
Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics

Glenn R. Gibson [™], Robert Hutkins, Mary Ellen Sanders, Susan L. Prescott, Raylene A. Reimer, Seppo J. Salminen, Karen Scott, Catherine Stanton, Kelly S. Swanson, Patrice D. Cani, Kristin Verbeke & Gregor Reid

Nature Reviews Gastroenterology & Hepatology 14, 491–502(2017) | Cite this article

"A substrate that is selectively utilized by host microorganisms conferring a health benefit."

The definition expands the concept of prebiotics to possibly include non-carbohydrate substances, applications to body sites other than the GI tract, and diverse categories other than food



Health effects of prebiotics

Include benefits to:

GI tract (inhibition of pathogens, immune stimulation, gut barrier permeability)

Cardiometabolism († insulin sensitivity, blood lipids)

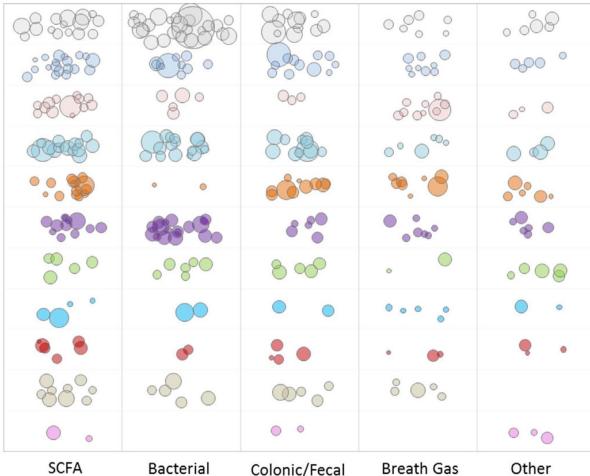
Mental health (metabolites that influence brain function and cognition)

Bone (↑ mineral bioavailability)



Health effect of prebiotics

Oligosaccharides Resistant Starch Cereal Fiber Chemically Synthesized Bran Inulin Fruit/Vegetable/Plant Gums & Mucilages Other NSP Combination **High Fiber Diet**



pН

Sawicki CM et al. *Nutrients* 2017;9:125

Scale (for reference)

Concentration



Composition

Excretion

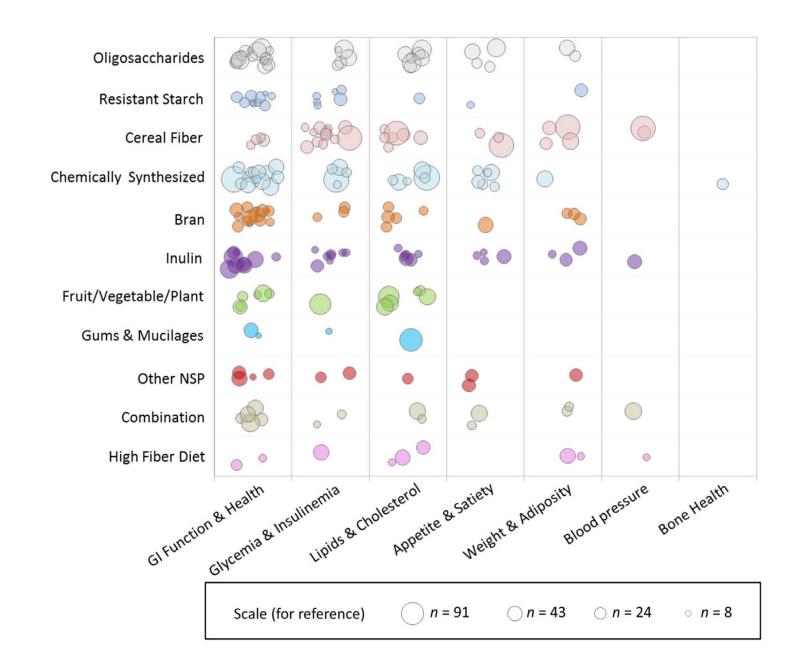
 $n = 136 \bigcirc n = 50 \bigcirc n = 12 \bigcirc n = 5$

Fermentation

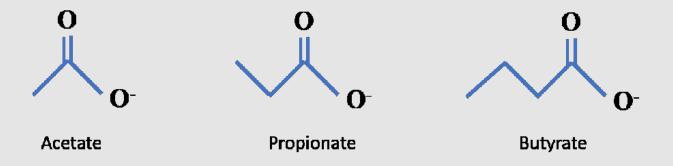
Markers

Health effect of prebiotics

Sawicki CM et al. *Nutrients* 2017;9:125



SCFAs (Short-chain fatty acids)

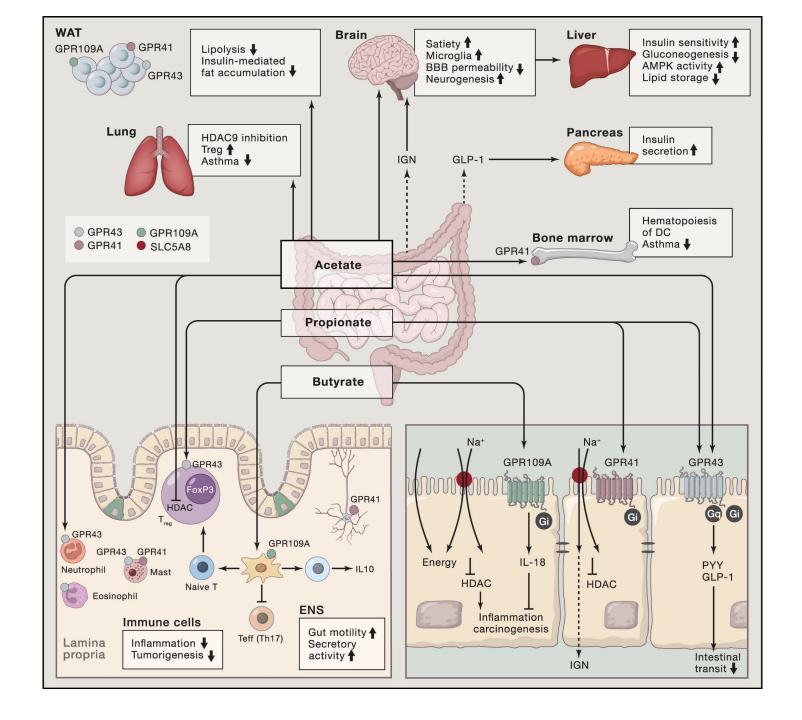


Metabolites of bacterial fermentation of prebiotic fibre and resistant starch

Used as an energy source by enterocytes and for microbial growth (butyrate) or transported into the bloodstream (acetate and propionate)

Modulate aspects of metabolic activity including colonocyte function (nutrient absorption, pH and motility), pathogen proliferation, intestinal barrier integrity, inflammation, blood lipids and appetite

SCFAs — it's complex



Grains and your gut

Grains contain various types of prebiotic fibres that serve as important fuels for the gut microbiota

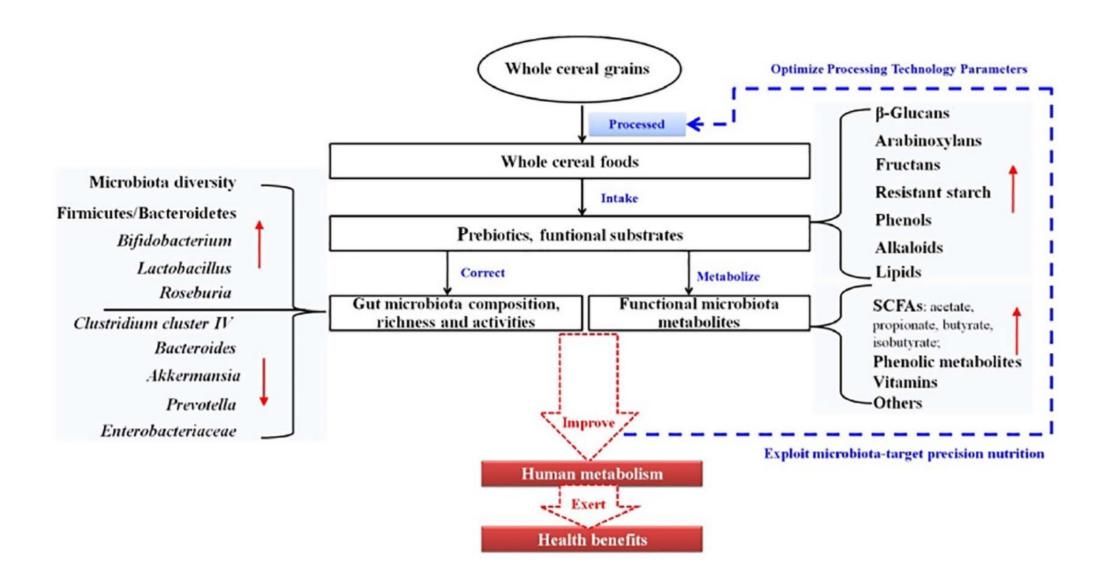
- Arabinoxylans
- Fructans
- Beta-glucan
- Resistant starch



Table 1 Definition and distribution of nondigestible carbohydrates in wheat (% dry matter)

Schematic representation								
Botanical components	Grain	Bran	Aleurone cells and germ	Starchy endosperm				
Milling fractions Arabinoxylan [2,19**]	Wholemeal Bran flour Aleurone flour White flour Carbohydrates consisting of β (1,4)-linked D-xylopyranosyl residues to which a-L-arabinofuranose units are linked as side chains. Some arabinoses can be substituted with ferulic acid. The degree of substitution refers to the arabinose moieties on the xylose backbone and is further also described as A/X ratio.							
	4-9%	12.7-22.1%	60-70%	1.4-2.8%				
Fructan [20-22]	linkages and har fructooligosacc	e an avDP of up to 19 wit	thout one glucosyl unit. Wheat fructans contain has a similar molecular weight distribution in the DP of $5-7$ in most whole grain whereas fructure -8 and ≥ 16 .	different fractions. Some				
	0.6-2.6%	2.7-3.7%	1.9%	1.5-1.6%				
β-Glucan [2,22,23]	residues separa	ted by single β (1,3)-linka	nopolymer arranged in blocks of consecutive ages. The chain mainly consists of cellotriosy blocks having more than four residues					
	0.5-1.4%	1.4-1.8%	0.9%	0.3-0.4%				
Resistant starch [24]	glucose residue -D-(1,6) linkage: intestine; it is r chemically treat	s are α -D-(1,4) linked, and s. Resistant starch is define neasured chemically as the digest ample and the digest	components, the amylose, which is essentially amylopectin, which is a larger branched moled as that fraction of dietary starch, which esca he difference between total starch obtained lible starch generated from nonhomogenized ons: RS1, RS2, RS3, and RS4.	cule with α -D-(1,4) and α pes digestion in the small from homogenized and				
	16.4%	1.1%	0.8% (in germ)					
Cellulose [2,22]	Cellulose is a h	omopolymer of glucose li	nked by β-(1,4) linkages only					
	<5% 8-10% 3.9% 0.5-0.							
Galactooligosaccharides [20,25]	molecular weigh pentasaccharide of sucrose.	t oligosaccharides, such a	lactosides or raffinose family oligosaccharides s raffinose (trisaccharide), stachyose (a tetrasades formed by α -(1,6)-galactosides linked to C	ccharide), verbascose (a				
	Identified	Not determined	Identified (raffinose: 7.2% in germ)	Not determined				

avDP, average degree of polymerization; DP, degree of polymerization.

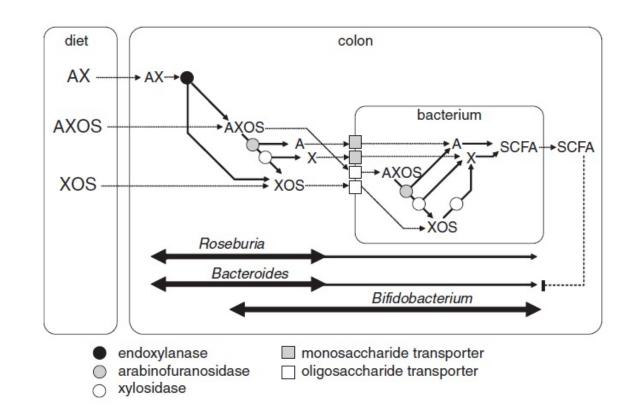


Arabinoxylans

Main non-starch polysaccharide in cereals and component of cell wall

Hydrolysis in the colon leads to arabinoxylan-oligosaccharides (AXOS) and xylo-oligosaccharides (XOS) formation

AXOS and XOS can 个 *Bifidobacteria* 个 SCFAs



Arabinoxylans

↑ stool frequency and improve stool consistency through effect of SCFAs ↑ absorption of salts and water into the bowel

Studies showing benefits on blood sugar, TGs and cholesterol

Animal studies show an anti-inflammatory and immune-enhancing effect



Fructans

Polymers of fructose found in wheat, barley, onions, garlic, agave, artichokes, asparagus and leeks

Includes:

- Inulin (11-60 chain length)
- Oligofructose (3-10 chain length) derived from inulin
- Fructo-oligosaccharides (3-5 chain length) derived from sucrose

Rapidly fermented by *Bifidobacterium* and *Lactobacillus* which are preferentially stimulated to grow, causing significant changes in the composition of the gut microbiota

Food item	Inulin	Oligofructose (as fraction of inulin)
Banana (fresh)	0.5	0.5
Asparagus (frésh)	2.5	2.5
Chicory root (fresh)	17.5	9.6
Garlic (fresh)	12.5	5.0
Jerusalem artichoke (fresh)	18.0	13.5
Leeks (fresh)	6.5	5.2
Onions (fresh)	4.3	4.3
Wheat bran (fresh)	2.5	2.5
Wheat flour (baked)	2.4	2.4
Barley(fresh)	0.8	0.8
Rye (baked)	0.7	0.7

Content of inulin and oligofructose (g/100 g; midpoint of reported ranges) in various foods

Fructans

Estimates that grains account for approximately 70% of daily fructan intake in Western diet

Wheat and barley fructans produce similar amounts of SCFAs as inulin



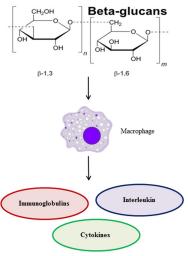
Beta-glucan

Polymers of glucose found grains, especially oats and barley

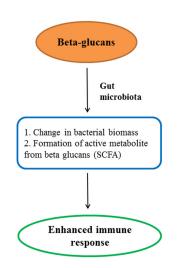
Can increase populations of Bifidobacterium and Lactobacillus in a dose-dependent manner

Increase SCFAs and immunoenhancing effects

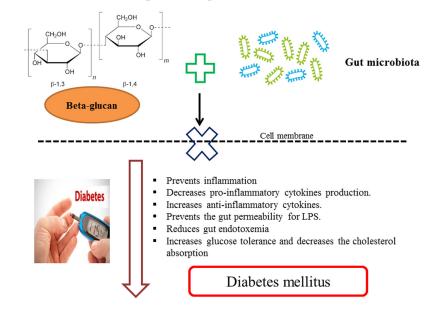
Favourable benefits on blood glucose could be mediated by gut microbiota



Beta-glucans activates the macrophages and release various immunoglobulins, interleukins and cytokines to defend the host against various pathogenic conditions Possible involvement of gut microbiota in beta-glucans immunomodulatory action



Influence of beta-glucan and gut microbiota on diabetes mellitus



Resistant starch

Component of dietary fibre

CSIRO estimates put RS consumption of Australian adults at 3 to 9 g/d

Goal of 15-20 g/d recommended for optimal bowel health

Designation	Description	Examples
RSI	Physically inaccessible starch	Coarsely ground or whole-kernel grains
RS2	Granular starch	High-amylose maize starch, raw potato, raw banana starch
RS3	Retrograded starch	Cooked and cooled starchy foods
RS4	Chemically modified starches	Cross-linked starch
RS5	Amylose-lipid complex	Stearic acid-complexed high-amylose starch

Resistant starch – health benefits

Functions like fermentable soluble fibre

Changes microbial composition

Fermented by bacteria to SCFAs

BSL regulation and improvement in insulin sensitivity

Appetite regulation via SCFAs effect on appetite hormones (leptin, GLP-1 and peptide YY)



An acute change in diet (going from strictly animal-based to plant-based diet) alters microbial composition within just 24 h, with reversion to baseline within 48 h of diet discontinuation

Published: 11 December 2013

Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David, Corinne F. Maurice, Rachel N. Carmody, David B. Gootenberg, Julie E. Button, Benjamin E. Wolfe, Alisha V. Ling, A. Sloan Devlin, Yug Varma, Michael A. Fischbach, Sudha B. Biddinger, Rachel J. Dutton & Peter J. Turnbaugh □

Nature **505**, 559–563(2014) Cite this article



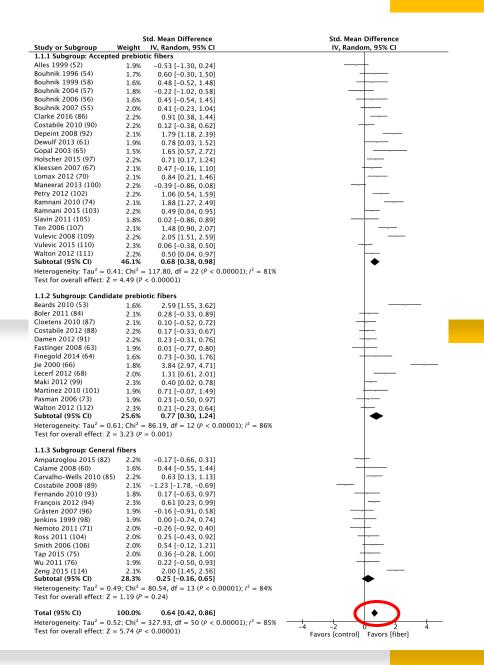
Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis

Daniel So, Kevin Whelan, Megan Rossi, Mark Morrison, Gerald Holtmann, Jaimon T Kelly, Erin R Shanahan, Heidi M Staudacher, Katrina L Campbell ▼

The American Journal of Clinical Nutrition, nqy041, https://doi.org/10.1093/ajcn/nqy041

Published: 11 May 2018 Article history ▼

Dietary fibre interventions \uparrow faecal abundance of *Bifidobacterium* and *Lactobacillus* as well as faecal butyrate concentration but did not affect α -diversity (number of distinct organisms)





ICD 2021 Cape Town Virtual @ICD2021CapeTown · 5h

What is the marker of a 'good' microbiota? Here are @ProfWhelan's "Microbiota Big 5" - Alpha diversity, Firmicutes: Bacteroidetes ratio, Bifidobacteria, Faecalibacterium prausnitzii and Akkermansia mucinophilia #ICD2021 #ICD2021Virtual

What is the marker of a 'good' microbiota?





Alpha diversity

Combination of the number (richness) of bacteria and evenness of distribution Diversity is lower in obesity, diabetes, IBS, inflammatory bowel disease

Lozupone, Nature. 2012; 489(7415): 220-30

Magne et al, Nutrients



Firmicutes: Bacteroidetes ratio

The two major phyla of bacteria in the gut Greater F:B ratio in people with low fibre intake and who are overweight

2020: 12: 1474



Bifidobacteria

Genus that colonises during infancy (HMO in breastmilk) and increased by prebiotics ower in many disorders of the gut (e.g. IBS, IBD)

Arboleya et al, Frontiers Microbiol. 2016: 7: 1204



Faecalibacterium prausnitzii

Species with immunoregulatory / anti-inflammatory properties Lower in people with IBD, and higher levels means longer remission

Miquel et al, Current Opinion Microbiology 2013, 16:255-261



Akkermansia mucinophilia

Species that impacts metabolism and insulin sensitivity. Preliminary evidence of beneficial impacts on body weight Cani et al, Frontiers Microbiol, 2017; 8: 1765

Microbiota Big 5

McBurney, J Nutr. 2019; 149: 1882-1895.









What do whole-diet intervention studies with wholegrains have to say about the gut microbiotahealth link?



Published: 23 October 2013

Carbohydrates, glycemic index and diabetes mellitus

Bifidogenic effect of whole-grain wheat during a 12week energy-restricted dietary intervention in postmenopausal women

EG Christensen, TR Licht, M Kristensen & M I Bahl

European Journal of Clinical Nutrition 67, 1316–1321 (2013) Cite this article

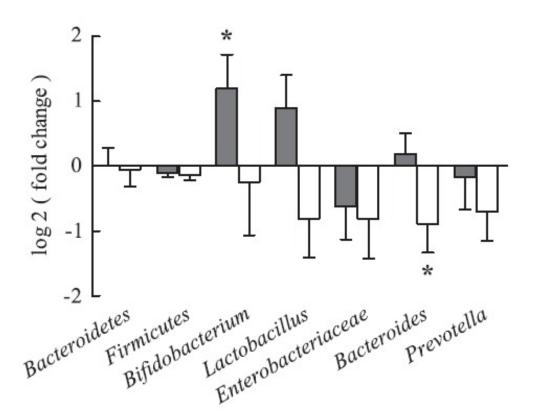
989 Accesses | 22 Citations | 3 Altmetric | Metrics

12-week parallel RCT in 79 women

Intervention of 105 g/d of wholegrain wheat to replace 2 MJ of habitual diet

Control group received refined-grain foods

Significant ↑ *Bifidobacterium*





Whole-grain wheat breakfast cereal has a prebiotic effect on the human gut microbiota: a double-blind, placebocontrolled, crossover study

Published online by Cambridge University Press: 29 August 2007

Adele Costabile, Annett Klinder, Francesca Fava, Aurora Napolitano, Vincenzo Fogliano, Clare Leonard, Glenn R. Gibson and Kieran M. Tuohy

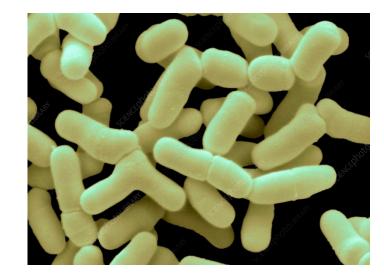
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Intervention of 48 g/d of wholegrain wheat cereal

Control group received refined-grain cereal

Significant \(\Delta \) Bifidobacterium and Lactobacillus



	Pre-WB		WB		Pre-WG		WG	
Bacterial group	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total bacteria	10.7	0-1	10.7	0.1	10-8	0.2	10-8	0.1
Bacteroides spp.	9.6	0.2	9.6	0.3	9.6	0.3	9.7	0.3
Eubacterium rectale group	10-1	0.2	10-0	0.2	10-0	0.1	10-1	0.1
Bifidobacterium spp.	8.9ª	0.4	8-8 ^b	0.4	8.5°	0.5	9-3a,b,c	0.4
Atopobium spp.	8.9	0.3	8.9	0.3	9.1	0.4	9.1	0.3
Cl. histolyticum/perfringens gp.	8-2	0.5	8.5 a	0.4	8.2ª	0.6	8-4	0.3
Lactobacilli/enterococci	8-0 ^{a,b}	0.4	8-4a,c,d	0.2	8-1 ^{c,e}	0.4	8.7 b,d	0.2

WB, wheat bran; WG, whole-grain.

abcd All values in one row with a common letter are significantly different from each other (P< 0.05, Tukey's post test).



Determination of the *in vivo* prebiotic potential of a maize-based whole grain breakfast cereal: a human feeding study

Published online by Cambridge University Press: 21 May 2010

Andrew L. Carvalho-Wells, Kathrin Helmolz, Cecelia Nodet, Christine Molzer, Clare Leonard, Brigid McKevith, Frank Thielecke, Kim G. Jackson and Kieran M. Tuohy

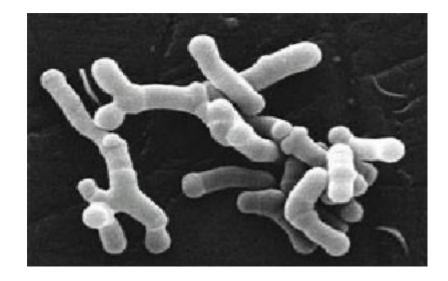
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3-week crossover RCT in 33 adults

Intervention of 48 g/d of wholegrain maize cereal

Control group received refined-grain cereal

Significant ↑ *Bifidobacterium*



	Pre WGM		Post WGM		Pre NWG		Post NWG		wo	
Bacterial group	Mean	\$D	Mean	SD	Mean	SD	Mean	SD	Mean	\$D
Bifidobacterium spp.	9.53ª	0.32	9-81 ^{a,b,c,d}	0.26	9-48 ^b	0-26	9.62°	0.33	9-48 ^d	0.20
Lactobacillus/Enterococcus group	8.78ª	0.25	8-87 ^{b,c}	0.27	8-69 ^b	0.27	8.77 ^d	0.26	8-52a,c,d	0.21
Atopobium cluster spp.	9-63a,b	0.27	9.94a,c	0.30	9-64 ^{c,d}	0.30	9.95b,d	0.26	9.75	0.23
Bacteroides - Prevotella spp.	9.96	0.33	9.95	0.29	10-01	0.38	10-03	0.33	10.03	0.25
REC cluster	9.90a	0.25	9.98°	0.22	9-90 ^b	0.25	10-07 ^{a,b,d}	0.29	9-80°.d	0.33
Clostridium histolyticum/perfringens gp.	8.42	0.33	8-35	0.33	8-43	0.33	8-42	0.26	8.52	0.29
Universal bacterial probe	10-81	0.22	10.94	0.27	10-74	0.34	10.92	0.28	10.76	0.29
Total cells	10.90	0.16	11.02	0.18	10.98	0.21	11.01	0.21	10.91	0.25

ORIGINAL RESEARCH article

Front. Microbiol., 07 November 2016 | https://doi.org/10.3389/fmicb.2016.01675



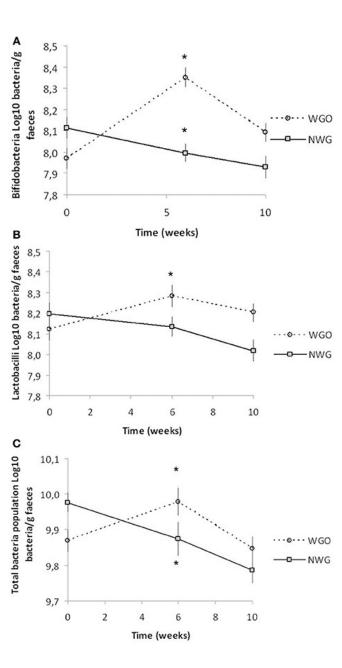
Hypocholesterolemic and Prebiotic Effects of a Whole-Grain Oat-Based Granola Breakfast Cereal in a Cardio-Metabolic "At Risk" Population

🕒 Michael L. Connolly^{1,2}, 🔛 Xenofon Tzounis^{1,2}, 🔛 Kieran M. Tuohy^{1,3*} and 🕒 Julie A. Lovegrove^{1,2*}

6-week crossover RCT in 32 adults
Intervention of 45 g/d of wholegrain oat cereal

Control group received refined-grain cereal

Significant \(\Delta \) Bifidobacterium and Lactobacillus



REPORT f ¥ in ⊕ № E

Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes



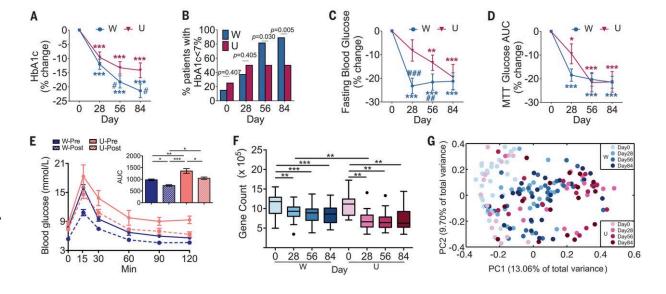
43 people with T2DM randomised to a diet high in traditional Chinese prebiotic foods and wholegrains or usual care regular diet for 3 m

Greater improvements in HbA1c and FPG in intervention group

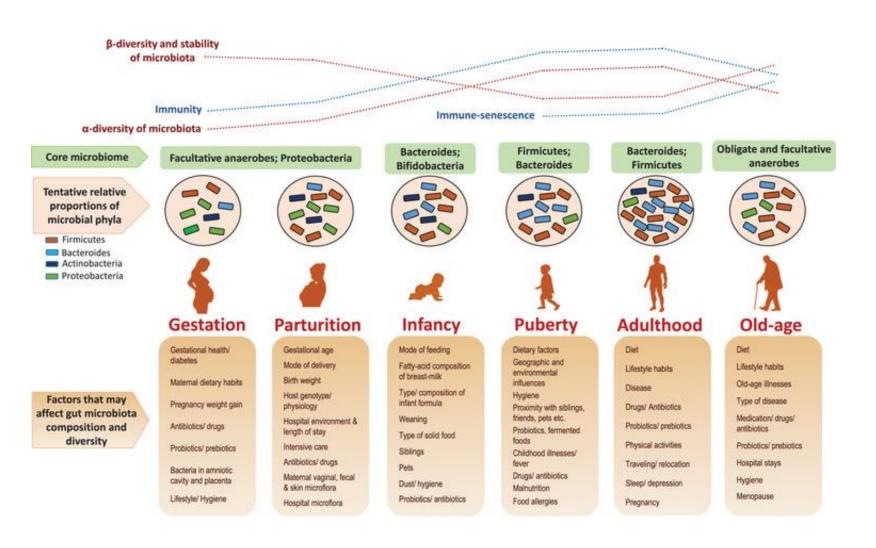
† gene diversity for carbohydrate metabolism and SCFA metabolism in intervention group

15 bacterial strains involved in SCFA production found at ↑ levels

Fibre $\rightarrow \uparrow$ specific gut bacteria $\rightarrow \uparrow$ SCFAs \rightarrow release of insulin secreting hormones







Going with the grain

Choose wholegrains where possible Smart swaps

- White crackers to whole grain crackers
- White bread to whole grain bread
- White rice to brown rice, barley or quinoa
- White flour to wholegrain flours such as wholemeal flour

Creative salads: try freekeh, brown rice, barley, buckwheat or even millet in your next salad

Blend it: add rolled oats into a smoothie



Going with the grain

Choose a wholegrain breakfast cereal

Choose wholegrain snacks

Experiment with different grains such as buckwheat, bulgur, millet, quinoa, sorghum, whole rye or barley

Mix up your flours when baking: swap out some of the white flour for wholemeal flour

If following a gluten-free diet, go for options such as millet, quinoa, buckwheat, sorghum or amaranth



Wrap Up

A wide variety of foods and substances are now considered prebiotics

Health effects of prebiotics are diverse and growing as the evidence base grows

Grains contain a unique mix of prebiotic fibres: arabinoxylans, fructans, beta-glucan and resistant starch which can change the gut microbiota and increase SCFA production

Dietary changes focussed on increasing more prebiotic fibre coming from wholegrain foods at a whole-diet level are effective in causing favourable gut microbiota changes



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