PERSPECTIVE

Perspective: Physiologic Importance of Short-Chain Fatty Acids from Nondigestible Carbohydrate Fermentation

Celeste Alexander,[1,3] Kelly S Swanson,[1,2] George C Fahey, Jr,[1,2] and Keith A Garleb[2,3]

[1]Division of Nutritional Sciences; and [2]Department of Animal Sciences, University of Illinois at Urbana-Champaign, Urbana, IL; and [3]Abbott Nutrition, Columbus, OH

ABSTRACT

In recent years, it has become increasingly obvious that dietary fiber or nondigestible carbohydrate (NDC) consumption is critical for maintaining optimal health and managing symptoms of metabolic disease. In accordance with this, the US FDA released its first official definition of dietary fiber in 2016 for regulation of Nutrition and Supplement Facts labels. Included in this definition is the requirement of an isolated or synthetic NDC to produce an accepted physiologic health benefit, such as improved laxation or reduced fasting cholesterol concentrations, upon consumption. Even though NDC fermentation and production of short-chain fatty acids elicit many physiologic effects, including serving as a source of energy for colonocytes, curbing glycemic response and satiety, promoting weight loss, enhancing mineral absorption, reducing systemic inflammation, and improving intestinal health, the process of fermentation is not considered a physiologic endpoint. Instead, expensive and laborious clinical trials must be conducted and an accepted physiologic benefit observed. In this review, we discuss the physiologic importance of NDC fermentation through extensive examination of clinical evidence and propose that the degree of fermentability of an NDC, rather than the endpoints of a clinical trial, may be appropriate for classifying it as a dietary fiber. *Adv Nutr* 2019;0:1–14.

Keywords: dietary fiber, fermentation, short-chain fatty acids, mineral absorption, gastrointestinal health

Introduction

In 2016, the USA FDA released its first official definition of dietary fiber in the regulations governing nutrition and supplement facts labels. According to the ruling, dietary fiber is defined as nondigestible soluble and insoluble carbohydrates with $\geq$3 monomeric units and lignin that are either intrinsic and intact in plants or isolated and synthetic and demonstrate a physiologic health benefit in humans (1). Dietary fiber includes a large collection of compounds that vary greatly in physicochemical properties, such as solubility, viscosity, and fermentability, and contribute to a variety of health benefits (2). Based on the 2016 definition of dietary fiber and the 2018 Declaration of Certain Isolated or Synthetic Nondigestible Carbohydrates as Dietary Fiber on Nutrition and Supplement Facts Labels, 15 isolated and synthetic nondigestible carbohydrates (NDCs) have been identified through scientific review by the FDA to provide $\geq$1 beneficial physiologic effect. Those include cellulose; pectin; guar gum; locust bean gum; hydroxypropylmethylcellulose; β-glucan; psyllium husk; mixed plant cell wall fibers; arabinoxylan; alginate, inulin, and inulin-type fructans (fructooligosaccharides); high-amylose starch/soluble corn fiber (resistant starch 2, RS2); galactooligosaccharides; polydextrose; and resistant maltodextrin/dextrin (1, 3, 4). Several isolated and synthetic NDCs are still being evaluated for accepted physiologic effects.

The 2015–2020 Dietary Guidelines for Americans recommend a daily intake of 14 g dietary fiber per 1000 kcal, although the majority of Americans fall far below this goal (5, 6). In the 1970s, it was hypothesized that a dramatic reduction in dietary fiber intake may be, in part, responsible for the increased incidence of many Western diseases (7). Since then, epidemiologic, preclinical, and clinical studies have demonstrated the beneficial effects of adequate dietary fiber intake on metabolic health. Currently, the FDA-accepted physiologic health benefits from fiber are the following: *1*) attenuation of blood glucose or insulin; *2*) lower fasting cholesterol concentrations; *3*) improved laxation; *4*) increased gastrointestinal (GI) mineral absorption; and *5*) reduced energy intake (increased satiety) (4). Production of fermentative end-products and changes in the GI microbiota are not currently considered physiologic endpoints, but

rather mechanisms by which a health benefit is produced (1). Until recently, the FDA only considered evidence from healthy populations when determining if an isolated or synthetic NDC confers a physiologic health benefit. This is especially problematic in cases of glycemic control and inflammation because healthy individuals generally do not have a physiologic need to curb these responses. Fortunately, in the 2018 guidance, the FDA announced that clinical trials in certain diseased populations would be considered and, thus, have been included in this review (4). All data summarized below were reported as being statistically significant ($P < 0.05$) unless stated otherwise. The purpose of this review is to discuss the physiologic importance of NDC fermentation through extensive examination of clinical evidence and propose that degree of fermentability should qualify NDCs to be labeled as dietary fibers.

Fermentation and Short-Chain Fatty Acids

Dietary fibers and NDCs vary greatly in their physicochemical properties, particularly fermentability. Although NDCs resist digestion by mammalian enzymes, many serve as substrates for fermentation by bacteria in the GI tract (2, 8). Collectively, the resident bacteria and other microorganisms in the GI tract are termed the "microbiota." The GI microbiota is one of the most densely populated microbial communities on earth, and contains ∼150 times more genes than the human genome (2, 9, 10). Insoluble NDCs (i.e., cellulose, hemicellulose, lignin) are generally low to moderate in fermentability and soluble NDCs (i.e., pectin, β-glucans, FOS, inulin, gums) tend to be highly fermentable, although the extent of fermentation varies greatly (11). The process of fermentation involves the hydrolysis of NDCs to their constituent sugars, which are subsequently fermented to produce primarily SCFAs, as well as H_2 and CO_2 gases (2, 12). Bacteria can hydrolyze numerous fibers through an extensive set of enzymes that are not produced in mammals—these belong to a large family of carbohydrate-active enzymes or "CAZymes" (2, 13). The degree of polymerization (also called chain length) and branching influence the rate and location of NDC fermentation. Greater degree of polymerization and branching are associated with a more sustained fermentation pattern throughout the large intestine, whereas shorter, less-branched NDCs are fermented more rapidly and proximally (2, 14, 15).

SCFAs produced from NDC fermentation include primarily acetate, propionate, and butyrate produced in an overall molar ratio of ∼60:20:20, respectively (11, 16). **Table 1** reports the molar ratios of SCFAs produced by in vitro fermentation with human fecal inoculum of some of the NDCs discussed in this review. SCFAs provide an energy source for microbial growth and a variety of physiologic effects for the host; thus, >90% of SCFAs are either metabolized by the microbiota for energy or absorbed by enterocytes (2, 10). Most SCFAs that are not metabolized by the microbiota are absorbed by enterocytes via passive diffusion or monocarboxylate transporter 1–mediated transport and into the circulation via solute carrier (SLC) family transporters, SLC5A8 and SLC5A12 (17). Once absorbed, SCFAs may be used by the enterocyte for energy or released into the portal circulation for utilization by peripheral tissues. Although acetate is the predominant SCFA found in the colon, butyrate is preferentially utilized by enterocytes as a source of energy and serves as a regulator of cellular proliferation and differentiation (11). On average, SCFAs provide ∼10% of daily caloric requirements of humans (18). However, this depends greatly on the amount of dietary fiber consumed daily, the proportion of fermentable fiber, and the composition of the GI microbiota.

Physiologic Benefits of Fermentation

Dietary fiber intake reduces the risk and symptoms of many metabolic and inflammatory diseases, including inflammatory bowel disease (IBD), cardiovascular disease, colorectal cancer (CRC), obesity, and diabetes (19). Fermentable NDCs elicit these benefits through production of SCFAs, which in addition to providing energy to colonocytes and resident bacteria, reduce GI luminal pH to directly limit pathogen growth, enhance mineral absorption, and promote bile acid excretion. SCFAs also act as secondary messengers that regulate gene expression and stimulate hormone and gut peptide synthesis [i.e., glucagon-like peptide 1 (GLP-1)], and initiate other signal transduction pathways in peripheral tissues (i.e., increased glucose utilization, reduced cholesterol synthesis) (10, 12, 20, 21). Although beyond the scope of this review, dietary fiber fermentation and SCFA production have been suggested to prevent neurodegeneration and promote regeneration (10, 22, 23). Butyrate specifically has been shown to act as a histone deacetylase inhibitor, increasing the expression of genes related to neural regeneration and plasticity (10, 23). Additionally, circulating SCFAs are able to cross the blood-brain barrier and alter neurotransmitter and hormone concentrations, affecting appetite (10, 22). The ability of fermentable NDCs and SCFAs, namely propionate, to reduce blood and hepatic lipid content has been extensively reviewed, and will thus not be discussed here (11, 16, 24). SCFAs also act as signaling molecules through

Perspective articles allow authors to take a position on a topic of current major importance or controversy in the field of nutrition. As such, these articles could include statements based on author opinions or point of view. Opinions expressed in Perspective articles are those of the author and are not attributable to the funder(s) or the sponsor(s) or the publisher, Editor, or Editorial Board of *Advances in Nutrition*. Individuals with different positions on the topic of a Perspective are invited to submit their comments in the form of a Perspectives article or in a Letter to the Editor.

The authors reported no funding received for this study.

Author disclosures: CA and KAG are employed by Abbott Nutrition. Abbott sells products containing nondigestible carbohydrates. The remaining authors have no conflicts of interest to report.

Address correspondence to CA (e-mail: calxndr3@illinois.edu).

Abbreviations used: AX, arabinoxylan; AXOS, arabinoxylooligosaccharide; BCFA, branched-chain fatty acid; CD, Crohn's disease; COS, chitosanoligosaccharide; CRC, colorectal cancer; CRP, C-reactive protein; DAI, disease activity index; DP, degree of polymerization; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; FOS, fructooligosaccharide; GBF, germinated barley foodstuff; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; GOS, galactooligosaccharide; GPCR, G-protein coupled receptor; HbA1c, glycated hemoglobin; IAUC, incremental area under the curve; IBD, inflammatory bowel disease; NDC, nondigestible carbohydrate; PHGG, partially hydrolyzed guar gum; PYY, peptide YY; RCT, randomized controlled trial; RK, rye kernel; RS, resistant starch; SCF, soluble corn fiber; SLC, solute carrier family transporters; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UC, ulcerative colitis; WBE, wheat bran extract; XOS, xylooligosaccharide.

TABLE 1 In vitro fermentation profiles of NDCs obtained with the use of human fecal inoculum[1]

NDC	Product/substrate	Ac:Pr:Bu (% total SCFA)	Total SCFA (mmol/g NDC)	Time (h)	Reference
Arabinoxylan	Wheat bran, Now Foods	60:33:07	4.94	8	Rumpagaporn et al. 2015 (25)
	Corn bran, Bunge Milling	75:17:08	7.51	8	Rumpagaporn et al. 2015 (25)
AXOS (wheat)	278 kDa, Megazyme	67:13:20	6.14	12	Hughes et al. 2007 (26)
COS (low molecular wt)	50–190 kDa, Aldrich	72:21:07	N/A	24	Vernazza et al. 2005 (27)
FOS (short chain)	NutraFlora, Ingredion	53:16:31	6.71	8	Hernot et al. 2009 (15)
FOS (medium chain)	Beneo P95	55:14:31	6.91	8	Hernot et al. 2009 (15)
	Beneo HP	58:14:28	6.46	24	Kaur et al. 2011 (28)
GOS	Vivinal GOS, Friesland Campina Domo	59:15:26	7.15	8	Hernot et al. 2009 (15)
Guar gum	Sigma	53:33:14	6.85	24	Bourquin et al. 1996 (29)
PHGG	Taiyo Kagaku Co Ltd	27:59:14	NA	8	Noack et al. 2013 (30)
	BeneFibra, GSK	35:27:38	NA	8	Carlson et al. 2015 (31)
Inulin	Oliggo-Fiber, Cargill	39:51:10	NA	8	Noack et al. 2013 (30)
	Oliggo-Fiber, Cargill	47:14:39	4.82	8	Hernot et al. 2009 (15)
	Beneo ST	44:13:43	5.91	8	Hernot et al. 2009 (15)
	Beneo HP	48:14:38	4.64	8	Hernot et al. 2009 (15)
	Beneo HP	58:14:28	3.2	24	Kaur et al. 2011 (28)
Inulin (FOS-enriched)	Beneo Synergy 1	45:14:41	6.16	8	Hernot et al. 2009 (15)
Pectin	Sigma	74:09:17	7.97	12	Campbell et al. 1997 (32)
Polydextrose	STA-LITE, Tate & Lyle	69:18:13	4.73	8	Hernot et al. 2009 (15)
Psyllium husk	Psyllium husk, P&G	56:32:12	0.76	12	Campbell et al. 1997 (32)
Soluble corn fiber	Promitor, Tate & Lyle	60:17:23	NA	72	Maathuis et al. 2009 (33)
Wheat dextrin	BeneFiber, GSK	34:52:14	NA	8	Noack et al. 2013 (30)
	BeneFiber, GSK	33:33:34	NA	8	Carlson et al. 2015 (31)

[1] Ac, acetate; AXOS, arabinoxylanoligosaccharide; Bu, butyrate; COS, chitosanoligosaccharide; FOS, fructooligosaccharide; GOS, galactooligosaccharide; NA, not available; NDC, nondigestible carbohydrate; PHGG, partially hydrolyzed guar gum; Pr, propionate.

the activation of G-protein coupled receptors (GPCRs), namely GPR41 and GPR43, and directly enhance nutrient absorption by reducing luminal pH and promoting growth of enterocytes. Based on our extensive review of clinical trials, it is becoming increasingly clear that these mechanisms play an important role in the ability of fermentable NDCs to help curb glycemic response, increase satiety and subsequent weight loss, increase mineral absorption, reduce chronic systemic inflammation, and promote GI health.

Glycemic Control, Satiety, and Weight Loss

One of the hallmark claims of dietary fiber consumption is the curbing of glycemic response and promotion of weight loss via increased satiety and decreased energy intake. Although reductions in postprandial glucose and energy intake are FDA-approved benefits of dietary fiber, some isolated, fermentable NDCs that may elicit these benefits are not currently considered by the FDA to be dietary fiber. Such NDCs include isomaltooligosaccharides, wheat fiber, glucomannan, and chitooligosaccharides. Although already considered fiber by the FDA, inulin and inulin-type fructans, GOS, high-amylose starch, pectin, guar gum, and β-glucan have been included in this review to support the position that glycemic control, satiety, and subsequent weight loss are mediated, in part, by fermentative end-products. The impact of fibers on glycemic response can be broken down into acute effects (those that occur within the same meal) and secondary effects (those that occur at a later meal, also called the second-meal effect). It is important to note that fiber viscosity has been shown to attenuate acute glycemic response by delaying gastric emptying and producing a physical barrier to nutrient absorption in the small intestine (34), and should be taken into consideration. However, the second-meal effect is thought to be mediated by SCFAs (35). As mentioned previously, SCFAs may bind GPCRs on enterocytes, enter the cells via diffusion or SLC5A8-mediated transport and act intracellularly, or enter circulation to bind GPCRs on distant tissues (10, 16, 36). Of particular relevance to glycemic control is the ability of SCFAs, particularly acetate and propionate, to bind and activate GPR43 and GPR41 on the brush border membrane. Upon activation, GPR41 and 43 stimulate the release of 2 satiety hormones: GLP-1 and peptide YY (PYY) from enteroendocrine L-cells (10, 36, 37). In addition to promoting satiety, these hormones stimulate insulin secretion and decrease glucagon secretion from the pancreas (16). Outside of the gut, SCFAs activate GPR41 and 43 on adipocytes, inducing expression of the anorexigenic hormone leptin (8, 10, 16, 36). Together, these actions of SCFAs implicate consumption of fermentable fibers with glycemic homeostasis and satiety that may result in subsequent weight loss.

Subjects with impaired glucose homeostasis

Perhaps the most important population of interest regarding glycemic control are individuals with impaired glucose homeostasis; those with prediabetes, type 1 and 2

diabetes mellitus (T1DM, T2DM), hyperinsulinemia, and often metabolic syndrome. Zhao et al. (38) observed that participants with T2DM who consumed ∼1900 kcal/d of a high-fiber diet (∼37 g fiber/d, 40% soluble fiber) for 12 wk lost more body weight (−4.2% compared with −1.5%) and had lower glycated hemoglobin (HbA1c) values (6.36% compared with 7.01%) than found in low-fiber diet controls (∼2000 kcal/d, ∼16 g fiber/d, 40% soluble fiber) with T2DM. Although both groups exhibited an increase in fecal acetate and a decrease in fecal pH, only the high-fiber group had greater concentrations of fecal butyrate as well as increased fecal abundance of genes involved in butyrate production. In the high-fiber group, the increase in SCFAs coincided with significantly greater postprandial GLP-1 compared with controls and fasting PYY concentrations compared with baseline. In a study conducted by Guess et al. (39), FOS-enriched inulin supplementation (30 g/d) in prediabetic subjects for 2 wk did not change postprandial glucose or insulin responses overall. Inulin-FOS supplementation resulted in greater weight loss than observed in cellulose controls (−7.6% compared with −4.9%, respectively), which corresponded with a decrease in kcal/d intake. Additionally, breath hydrogen concentration, an indicator of fermentation, was increased in the experimental group compared with control. However, when participants were split into either impaired-fasting glucose (IFG) or impaired-glucose tolerance (IGT), post-hoc analysis revealed that the IFG group had a reduced HOMA-IR and decreased fasting insulin concentration following FOS/inulin supplementation compared with IGT. A 2015 study conducted by the same group (40) observed that the same FOS-enriched inulin (30 g/d) did not affect insulin response in overweight or obese prediabetic individuals after 6 wk. However, the inulin-FOS again resulted in moderate but greater weight loss compared with controls, −0.42 kg compared with +0.38 kg. No difference in energy intake was observed at a single ad libitum meal at the end of the study, but it is unclear if regular dietary records were collected to assess differences in energy intake throughout the 18-wk intervention period. Although the glucose incremental area under the curve (IAUC) was lower in the inulin-FOS group following intervention, this effect was not present once adjusted for weight loss. Additionally, after 18 wk, breath hydrogen concentrations were greater in the FOS-enriched inulin group compared with control, indicative of increased fermentation.

Chitosanoligosaccharides (COSs) are derived from naturally occurring chitosan polymers in the chitin shells of crustaceans. Low-molecular-weight COSs have been shown to produce SCFA profiles similar to FOS in vitro (41). In adults with prediabetes, daily supplementation with just 1.5 g COS for 12 wk reduced body fat, waist circumference, postprandial glucose at 30 and 60 min, and plasma HbA1c concentrations compared with a matched roasted-barley meal control. Total energy intake was not different between groups (42). With promising findings at such a low dose, additional clinical trials are warranted to further understand the effects of COS on glycemia and weight loss in populations with impaired glucose homeostasis.

In a randomized controlled trial (RCT) parallel study with 90 T2DM participants, Kwak et al. (43) observed that supplementation of 6.5 g/d resistant corn starch for 4 wk reduced fasting insulin, HOMA-IR, and both glucose and insulin IAUC in response to a standard meal following the intervention period. Freeland et al. (44) supplemented hyperinsulinemic adults with 24 g/d wheat fiber for 12 mo and observed increased postprandial plasma GLP-1, acetate, and butyrate concentrations, but no changes in postprandial glucose or insulin. Lastly, Hartvigsen et al. (45) reported that a test meal containing a 5 g mixture of concentrated arabinoxylan (AX) and rye kernels (RKs), also high in AX, reduced acute glucose and insulin responses ($IAUC_{0–120\ min}$) and feelings of hunger ($IAUC_{0–360\ min}$) compared with the control meal. Plasma SCFA concentrations, specifically acetate and butyrate, were also greater after 360 min in the AXRK group compared with controls. However, no effect on the second-meal glucose response was observed following one-time supplementation with 5 g of AX, RK, or AXRK. Long-term supplementation with AX may affect glycemic response via adaptation to fiber consumption.

Overweight or obese subjects without impaired glucose homeostasis

Other populations of interest are overweight or obese individuals who do not have impaired glucose homeostasis. Interventions with FOS, GOS, and inulin have shown mixed results in this population. Savastano et al. (46) observed that a daily mixture of FOS and pectin, 5 g each, did not produce any changes in energy intake, satiety, or glucose tolerance in overweight or obese adults after 22 d. Another study observed that 8 wk of FOS supplementation, at 30 g/d distributed across 3 meals, increased circulating SCFAs and tended to increase PYY IAUC. However, there were no effects on glucose or insulin IAUC. Hunger scores and motivation to eat were decreased following the FOS supplementation (47). Morel et al. (48) reported that αGOS dose (6, 12, or 18 g/d), but not degree of polymerization (high content of DP2 compared with DP3 compared with DP4), increased satiety and decreased energy intake in overweight adults after 2 wk. Additionally, those in the 12- and 18-g/d treatment groups had a greater reduction in weight, BMI, and fat mass after 2 wk than observed in the control group. In a study by Chambers et al. (49), primary human colonic cells in culture were used to determine that propionate administration promotes the production of PYY and GLP-1. Following this, the group developed a novel inulin-propionate ester for targeted delivery of propionate to the colon and conducted both an acute, 6-h clinical trial and a 24-wk RCT crossover trial in overweight adults. They demonstrated that acute supplementation of 10 g of the novel ester increased postprandial plasma propionate, PYY, and GLP-1 concentrations, and reduced energy intake compared with 10 g of inulin alone. Following the 24-wk intervention, the inulin-propionate ester group had reduced

weight gain and intra-abdominal adipose tissue (−0.1% compared with +0.5%) compared with the inulin control group. Interestingly, the ester group prevented the deterioration in insulin-sensitivity that was observed in the inulin control group.

Few experiments have investigated the effectiveness of RS and nonfructan fermentable NDCs in improving satiety and acute glycemic homeostasis in overweight, normoglycemic adults. Bodinham et al. (50) reported that 4 wk of 40 g/d high-amylose-resistant starch supplementation resulted in increased first-phase insulin secretion, which is usually impaired in individuals with T2DM, following an intravenous glucose tolerance test. The increase in insulin secretion was not accompanied by a significant reduction in blood glucose concentrations following the intravenous glucose tolerance test, which would suggest a decrease in insulin sensitivity. However, when insulin sensitivity was measured, there was no difference between groups. In overweight women, Lafond et al. (51) observed that meals containing 15 g of either enzyme-hydrolyzed or intact AX in flax increased postprandial GLP-1 and PYY compared with a low-fiber, isocaloric control. Additionally, the 4-h insulin IAUC was lower in both fiber treatments than in the low-fiber, nonisocaloric control, but not compared with the isocaloric control. Li et al. (52) observed that 34 g/d of NUTRIOSE, a glucose polysaccharide derived from maize and wheat, decreased fasting glucose, insulin, HOMA-IR, and HbA1c in overweight men after 12 wk. A recent study conducted by Rahat-Rozenbloom et al. (53) reported that one-time supplementation with 24 g inulin increased serum SCFA concentrations, but did not affect acute or second-meal glucose and insulin responses. One-time resistant cornstarch supplementation at 28 g, however, reduced second-meal glucose and insulin responses without increasing serum SCFAs. Steady fermentation of RS over a long period of time, rather than rapid fermentation of fructans such as inulin, may provide sustained SCFA production that elicits a second-meal effect without influencing nonportal circulating SCFA concentrations.

Healthy subjects

The majority of clinical trials involving dietary fiber, weight loss, and glycemic response have been conducted in healthy individuals. This is problematic when studying glycemic control because healthy individuals generally do not have a physiologic need to curb the glycemic response or lower fasting concentrations of related metabolites and hormones. Nevertheless, it is important to consider evidence from all populations. Inulin and FOS have been heavily studied in healthy individuals, and have been found to increase satiety and postprandial circulating GLP-1 (54–56). Tarini et al. (55) reported that a single meal containing 24 g inulin increased plasma GLP-1 after 30 min, and resulted in decreased ghrelin concentrations after 4.5 h. An increase in serum SCFA concentrations was also observed after 4 h, but postprandial glucose and insulin remained unaffected. In 2015, Morris et al. (57) reported that one-time supplementation with 8 g FOS or inulin was insufficient to reduce satiety, ghrelin, or energy intake. Because an increase in breath hydrogen following inulin supplementation was observed compared to the control, a longer intervention period may have influenced these parameters. Two parallel RCTs demonstrated that FOS supplementation at 16 g/d for 2 wk increased postprandial plasma GLP-1 and PYY and decreased hunger rates (54, 56). In one of the studies, these findings were strongly correlated to positive breath hydrogen tests, suggesting the role of fermentation (54).

Nonfructan type NDCs have also been shown to be effective in healthy populations. AXOS supplementation at 6 or 12 g for a single meal reduced glucose and insulin IAUC in a dose-dependent manner. Reduction in both glucose and insulin suggest improved insulin sensitivity (58). Wanders et al. (59) reported that 10 g gelled pectin, a less viscous form of pectin, decreased hunger and desire to eat after both a single meal and 2 wk of daily intervention. Reduced energy intake and elevated breath hydrogen concentrations were only observed after a single meal. A 1-d supplementation of 60 g RS (Novelose 260) produced a second-meal effect of reduced plasma glucose and insulin and improved insulin sensitivity the following morning when a controlled fiber-free breakfast was consumed. Breath hydrogen concentrations were greater during the breakfast meal in the RS group, suggesting sustained fermentation throughout the night. Despite this, nonportal plasma SCFAs were not different between groups; however, this is unsurprising for steady, sustained fermentation of RS (60).

Summary

Collectively, these findings suggest that fermentable NDCs have the ability to improve insulin resistance/sensitivity, decrease postprandial glucose elevation, and reduce HbA1c in populations with impaired glycemic homeostasis. Fermentable NDCs also increase satiety and reduce energy intake with accompanied weight loss in otherwise healthy overweight or obese individuals. In healthy, lean individuals, fructan-type NDCs are effective in increasing satiety and postprandial GLP-1. However, many previous studies investigating the effect of viscous fermentable fibers in several different populations have not measured indicators of fermentation, such as circulating or fecal SCFAs, fecal pH, or breath hydrogen concentration (61–70). Thus, future clinical trials are warranted. Additionally, viscous fibers (guar gum and hydroxypropyl methylcellulose) have been shown to reduce adiposity/fat mass in rats regardless of fermentability, suggesting that fermentation does not have an additive effect with viscosity with regard to weight loss (71). Therefore, clinical interventions with fibers having both low- and high-viscosity forms (i.e., guar gum compared with PHGG) are needed to isolate the effects of fermentation on glycemic response and satiety from those of viscosity for NDCs such as guar gum, pectin, and some RSs.

Mineral Absorption and Balance

Mineral consumption and absorption is essential for maintaining health and growth. Increasing mineral absorption, retention, and balance is an additional function of fermentable NDCs. Studies have shown that fermentable fibers may increase the absorption of several minerals in humans. Proposed mechanisms for the enhancement of mineral absorption by fermentable NDCs predominantly involve the production of SCFAs. Some of these mechanisms include: increased solubility of minerals due to decreased luminal pH; trophic effects of SCFAs on enterocytes, increasing absorptive surface area; and increased folate production via increases in *Bifidobacterium*, which is associated with higher bone mineral density and bone mineral content in postmenopausal women (21, 72). Evidence from humans most strongly supports enhanced absorption of Ca and Mg, and possibly Fe.

Postmenopausal women

These benefits are particularly important in women's health due to increased bone demineralization and total bone loss following menopause (73). Although Tahiri et al. (74) did not observe an increase in Ca absorption with the use of stable-isotope methods in postmenopausal women following short-chain FOS supplementation at 10 g/d, Slevin et al. (75) observed that short-chain FOS + Ca supplementation (derived from algae) for 2 y reduced the decline in bone mineral density. Additionally, a slowed rate of total bone loss was observed in a subgroup of the participant pool that had osteopenia, compared with the maltodextrin control group. These data suggest that in postmenopausal women, prolonged fermentable NDCs and mineral cosupplementation may be an effective method for slowing loss of bone and mineral density. Holloway et al. (76) observed increased Ca and Mg absorption, as well as increased bone formation, in postmenopausal women receiving 5 g/d of FOS-enriched inulin for 6 wk, compared with the maltodextrin control group. SCF, at 10 or 20 g/d for 50 d, also has been shown to increase bone Ca retention and bone Ca balance in a dose-dependent manner in postmenopausal women (77). In contrast, 15 g wheat dextrin/d was observed to have no impact on Ca or Mg absorption in a group of pre- and postmenopausal women (78).

Children and adolescents

Children and adolescents are populations of interest regarding mineral absorption to ensure development of optimal peak bone mass to prevent risk of osteoporosis later in life (79). Paganini et al. (80) reported that cosupplementation of Fe (a mixture of ferrous fumarate and sodium iron EDTA) and 7.5 g GOS/d increased Fe absorption in Kenyan infants compared with Fe supplementation alone. This change was negatively correlated with fecal pH, suggesting a potential role of SCFA production. Sanwalka et al. (81) showed that 1 dose of a FOS/GOS blend (8 g) with a meal increased Ca absorption in adolescent girls. Other RCT crossover studies have also shown increases in Ca absorption following FOS or inulin-enriched FOS supplementation in both male and female healthy adolescents (age 9–16 y) at doses ranging from 8 to 15 g/d, compared to maltodextrin or sucrose controls (82–85). Abrams et al. (84) found the absorptive benefit of the inulin-enriched FOS was comparable to an increase in daily Ca intake by 250 mg (~19% of the RDA for this age group).

The degree of polymerization (DP) affects the fermentative behavior of fermentable NDCs, with longer-chain fibers being fermented slowly throughout the distal small intestine and large intestine compared with the rapidly fermented fibers that largely disappear in the proximal region (86). Griffin et al. (85) reported that 3 wk of supplementation with 8 g FOS/d alone did not affect Ca absorption; however, 8 g/d of inulin-enriched FOS (ORAFTI Synergy 1) increased Ca absorption compared with the placebo group (38.2% compared with 32.3%, respectively). Because long-chain inulin (DP: 25) was used in this blend, it may be hypothesized that slower rates of fermentation and, thus, prolonged SCFA production, contribute to increases in mineral absorption. However, a RCT parallel study conducted by Martin et al. (87) demonstrated that the same inulin-FOS blend had no impact on Ca absorption or retention in adolescent girls. Another study reported that 10 g/d of FOS supplementation did not impact Ca, but increased Mg absorption in adolescent girls with habitual low Ca intake (79).

SCF has also been shown to improve Ca absorption in adolescent boys and girls. In a double-blinded RCT crossover trial, Whisner et al. (88) reported that 12 g/d supplementation of SCF to diets containing suboptimal Ca increased absorption of Ca by 12% compared with the control group; however, Ca retention, fecal Ca, and urinary Ca were unaffected. The observed increase in Ca absorption was positively correlated to an increase in *Bacteroides*, highlighting the potential link between absorption and fiber fermentation. In 2016, the same group demonstrated that supplementation of 10 or 20 g SCF/d in free-living female adolescents increased Ca absorption by 13.3% and 12.9%, respectively. Fecal pH was lower in the 20-g/d group, although fecal SCFA concentrations did not differ (89).

Healthy subjects

Many studies performed in healthy adult humans support the previously described findings. Coudray et al. (90) observed an increase in Ca absorption following inulin supplementation (40 g/d) in healthy young men, with no changes in Mg, Fe, or Zn absorption. Conversely, van den Heuvel et al. (91) observed that 15 g/d of inulin, FOS, or GOS did not impact Ca or Fe absorption in the same population. These data suggest that in healthy young males, 15 g/d fermentable NDC supplementation may not be sufficient to produce significant results. In women with low Fe status, inulin supplementation (20 g/d) tended (P = 0.10) to increase Fe absorption, but did not reach statistical significance despite producing a lower fecal pH and increasing fecal *Bifidobacterium* (92). Weinborn et al. (93) observed that as little as 2 g/d of a prebiotic blend (inulin, polydextrose, arabic gum, guar gum) supplemented with 3 mg/d of labeled heme Fe (isolated from

Holstein Friesian calves) increased the bioavailability of the heme Fe by 56% compared with the group supplemented with labeled heme Fe alone. Vermorel et al. (94) reported that a 5-d supplementation (following a 20-d adaptation) of 100 g/d of NUTRIOSE FB, a purified, fermentable wheat dextrin, distributed across 6 meals and snacks increased Mg absorption (%) and retention (mg/d), and tended to increase Ca absorption (P = 0.09). The NUTRIOSE FB supplementation had no impact on Zn balance. Although some participants experienced digestive symptoms, such as excessive gas and abdominal pain, these diminished after 20 d of adaptation. In the only study investigating the impact of pectin on Ca balance, 36 g/d did not result in any effect. However, this was a nonrandomized, controlled trial with only 5 participants, so these results may have been confounded by several sources of variation (95).

Nonfermentable and poorly fermentable fibers

Some studies testing insoluble or poorly fermentable fibers, such as bran and psyllium (96, 97), have demonstrated a lack of effect, or even a negative effect on mineral absorption, further suggesting that enhancement of mineral absorption is a benefit of fermentation and SCFA production. Heaney et al. (98) demonstrated that 3.4 g psyllium supplementation for 4 wk (Metamucil) in postmenopausal women did not affect Ca absorption. Balasubramanian et al. (99) showed that supplementation of 10 g of bran at each meal (30 g/d total) decreased Ca absorption from 22.1% to 8.6% in adults aged 59–76 y. O'Brien et al. (100) showed that high-fiber diets (13.4 g fiber/kg diet) rich in bran also resulted in reduced Ca absorption in healthy males aged 21–33 y compared with low-fiber diet (2.8 g fiber/kg diet) controls despite no differences in daily energy intake (37.1% compared with 60.6%, respectively). Other studies investigating bran supplementation in adult men at 22 g/d (101) and 10.9 g/d (102) showed no change in overall mineral balance. Lack of or negative effects are likely mediated by the phytate content of these fibers (103).

Summary

The current evidence indicates that nonfermentable and poorly fermentable fibers do not improve mineral absorption. Instead, it is clear that highly fermentable fibers enhance mineral absorption and retention—particularly Ca and Mg. Some studies have shown that increased mineral absorption is correlated to increases in specific microbial taxa and decreases in fecal pH, supporting the notion that these effects are a direct result of SCFA production. Future clinical studies would benefit from implementing more of these correlative analyses. Further investigation is needed regarding the impact of fermentable fibers on absorption of other minerals, such as Fe, Zn, K, and P. Although the existing evidence supports the ability of fermentable fibers to increase some mineral absorption and retention, the majority of this research has been conducted in healthy or nonrisk participants who typically do not have a physiologic need for increasing mineral status.

Gut Health and Inflammation

It has become increasingly evident that the GI tract, particularly the colon, is involved in much more than simple digestive and absorptive functions. Compromised GI health and chronic, low-grade inflammation often occur together, and are linked to a decline in overall health and an increased risk of disease development (11). Gut health is commonly assessed by measures of motility (transit time, stool frequency, stool consistency), histology (morphology, epithelial proliferation, immune cell infiltration), permeability (lactulose:mannitol excretion ratio), endoscopy, fecal metabolites (ammonia, BCFAs, SCFAs, IgA), and serum metabolites (zonulin). More recently, GI health also has been assessed via microbiota taxonomy, namely by increases in abundance of potentially beneficial taxa such as *Bifidobacterium* and *Lactobacillus*, and decreases in abundance of potentially harmful taxa such as *Clostridia*. Systemic inflammation is most commonly assessed by measuring circulating immunologic molecules, including cytokines (TNF-α, INF-γ), interleukins (IL-1β, IL-6, IL-8, IL-10), and acute phase proteins [C-reactive protein (CRP), serum amyloid A], endotoxins (LPS), and markers of oxidative stress (oxidized LDL, malondialdehyde). SCFAs produced from NDC fermentation contribute to maintenance of GI health and inflammation. Butyrate is the preferred energy source of colonocytes and stimulates growth of the colonic epithelium. SCFAs also activate GPR41, GPR43, and GPR109A in the small intestine, colon, and immune cells to mediate gut and immune cell growth and differentiation, gut motility and permeability, and production of immunologic proteins (10). In contrast, products of protein fermentation—ammonia, BCFA, H_2S, phenols, and indoles—are generally considered toxic for gut health as they have been shown to increase gut permeability and are associated with increased incidence of CRC (104–106). However, recent evidence suggests that some tryptophan-derived indoles, particularly indole-3-propionic acid, may improve gut barrier function (107, 108).

Inflammatory bowel disease

Inflammatory bowel disease, which primarily includes ulcerative colitis (UC) and Crohn's disease (CD), is a group of chronic inflammatory disorders affecting the GI tract (109). In IBD, increased gut permeability results in increased translocation of inflammatory stimuli in the lamina propria, triggering an immune response (110). Because SCFAs have multiple beneficial effects on the gut barrier, it has been hypothesized that SCFA enemas or consumption of fermentable fibers may help to relieve symptoms of IBD and prevent relapse. SCFA enemas, which have been studied since the 1990s, have been shown to be particularly beneficial in UC patients specifically because this disease primarily affects the distal colon. In 1992, Scheppach et al. (111) demonstrated that 100 mL sodium butyrate enemas twice per day for 2 wk decreased stool frequency and stopped

discharge of blood in 9 out of 10 patients with unresponsive UC. Further evidence to support the use of butyrate enemas in treating UC was published in 2002 by Lührs et al. (112). They observed that, compared with placebo enemas, 60-mL doses (100 mM sodium butyrate), twice daily for 8 wk, reduced activation of NF-κB in lamina propria macrophages (11.5% compared with 72.4%) as well as the number of neutrophils in the crypt (−0.8 compared with +0.3) and surface epithelia (−0.5 compared with 0.0) and lymphocytes in the lamina propria (−0.6 compared with −0.3). Additionally, these findings were correlated with lower disease activity indices (DAIs) compared than the placebo group after 8 wk (∼0.5 compared with ∼5.0, on a scale of 0–10). A few studies have also investigated the success of mixed SCFA enemas in treatment/management of UC. Vernia et al. (113) reported that a mixed 100-mL enema of sodium acetate, sodium propionate, and sodium butyrate (120 mM total) twice daily for 6 wk led to a decrease in bowel movement urgency and improved endoscopic scores, histologic scores, and self-evaluations compared with baseline, whereas the placebo group showed no differences from baseline. In contrast, another study reported that neither mixed SCFAs (130 mM) nor butyrate (100 mM) enemas dosed twice daily at 60 mL for 8 wk had an effect on humoral parameters of inflammation, including erythrocyte sedimentation rate and serum CRP, *O*-acid glycoprotein, haptoglobin, and Fe in patients with distal UC (114). However, the butyrate enema group had fewer patients with affected colonic segments than the placebo group at the end of the study.

In addition to SCFA enemas, dietary supplementation of fermentable fibers, particularly FOS or germinated barley foodstuff (GBF), have been shown to be effective in modulating symptoms and remission of CD and UC. Benjamin et al. (115) showed that supplementation with 15 g FOS/d decreased the proportion of IL-6-positive and increased the proportion of IL-10-positive dendritic cells in the lamina propria (+0.7 compared with +0.2 intensity ratio) of CD patients compared with baseline. The placebo group showed no changes from baseline. GBF is a prebiotic product derived from fractions of germinated barley and produces predominantly butyrate when fermented in the GI tract (116–118). In 1998, Mitsuyama et al. (116) conducted a pilot study in which 10 UC patients were given 30 g GBF/d in addition to conventional drug therapy for 4 wk. They observed improved clinical activity indices (6.9 to 2.8) and endoscopic scores (6.1 to 3.8), as well as increased fecal butyrate concentrations, at the end of the study. In a 12-mo randomized, controlled trial, 20 g/d GBF supplementation resulted in improved clinical activity indices at 3-, 6-, and 12-mo time points compared with controls. In addition, the cumulative recurrence rate was lower in the GBF group than controls, suggesting that GBF supplementation may prolong remission in UC patients (119). Supplementation of 30 g GBF/d for 2 mo also has been shown to decrease abdominal pain and cramping, as well as serum IL-6, IL-8, and CRP compared with baseline, whereas the control group showed no change (117, 118). It is important to note studies have also shown that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) may be beneficial in modulating symptoms, particularly abdominal pain and bloating, in patients with IBD (120). Although a low-FODMAP diet reduces the severity of GI symptoms, SCFA enemas and fermentable fibers reduce indices of GI inflammation and prevent relapse.

Metabolic dysfunction

Individuals with excessive body fat, metabolic syndrome, or diabetes often exhibit systemic, low-grade inflammation and oxidative stress, indicated by an increase in proinflammatory biomarkers such as serum CRP, complement C3, IL-6, TNF-α, and LPS, and decreased anti-inflammatory markers such as serum IL-10. Chronic low-grade inflammation is often implicated in the development of chronic diseases, including diabetes, cardiovascular disease, fatty liver disease, and cancer (48, 121–123). Thus, dietary interventions that reduce chronically elevated systemic inflammation are of great interest to promote health. Several studies have investigated the impact of fermentable fiber consumption on markers of inflammatory status in individuals who are overweight, obese, or have metabolic syndrome. Consumption of legumes rich in fermentable fibers has been associated with decreased waist circumference and lower blood pressure (121, 124). Hermsdorff et al. (121) reported that a hypocaloric diet rich in legumes resulted in greater loss of body weight (−7.8% clinical activity indices −5.3%) as well as a greater reduction in serum CRP (−1.2 clinical activity indices +0.4 mg/dL) and complement C3 concentrations compared with the control hypocaloric diet after 8 wk. These reductions in inflammatory markers remained greater in the legume diet group even when adjusted for weight loss. A different study examined the impact of single experimental meals—black bean meal, fiber-matched meal, or antioxidant-matched meal—on markers of oxidative stress and inflammation in adults with metabolic syndrome. Although no differences were observed in postprandial plasma oxidized LDL among groups, the black bean meal resulted in greater plasma concentrations of VCAM1, an adhesion molecule used as a marker of vascular inflammation, than found in the other meals. However, it has been suggested that adhesion molecules are not consistently altered following meals, and therefore they may not be the most accurate indicators of postprandial inflammation (125).

Prebiotic GOSs have been shown to modulate inflammation in overweight adults. In a randomized, controlled, double-blind, crossover trial, a mixture of trans-GOS supplemented at 5.5 g/d for 12 wk decreased plasma CRP and fecal calprotectin, a marker of neutrophil infiltration in the GI mucosa. Trans-GOS also increased fecal concentrations of bifidobacteria and IgA, which are involved in fiber fermentation and protection of gut barrier function, respectively (126). Additionally, variable doses (6, 12, or 18 g/d) of α-GOS all have been shown to reduce plasma LPS and

TABLE 2 Summary of key findings[1]

Glycemic control, satiety, and weight loss	
Subjects with impaired glucose homeostasis	Improved insulin resistance/sensitivity, decreased postprandial glucose elevation, reduced HbA1c
Overweight or obese subjects without impaired glucose homeostasis	Increased satiety and reduced energy intake with accompanied weight loss
Healthy subjects	Increased satiety and postprandial GLP-1 concentrations
Mineral absorption and balance	
Postmenopausal women	Reduced decline in bone mineral density, slowed rate of total bone loss, and increased Ca and Mg absorption, bone formation, bone Ca retention, and bone Ca balance
Children and adolescents	Increased absorption of Fe, Ca, and Mg
Healthy subjects	Increased Ca and Mg absorption, increased Mg retention, increased heme Fe bioavailability
Gut health and inflammation	
Inflammatory bowel disease	Improved DAI and histologic scores, prolonged remission, decreased stool frequency, reduced proportion and activation of GI-resident inflammatory cells, reduced circulating inflammatory marker concentrations
Metabolic dysfunction	Weight loss, reduced circulating inflammatory and oxidative stress marker concentrations, reduced immune-cell infiltration in the GI tract
Healthy subjects	Decreased fecal ammonia concentrations, decreased β-glucuronidase activity, improved measures of GI permeability, reduced circulating inflammatory marker concentrations, decreased protein fermentation

[1] DAI, disease activity index; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin.

CRP compared with a glucose control after only 2 wk of intervention in overweight adults (48).

The ability of inulin alone or inulin enriched with FOS to attenuate inflammation in women with impaired glycemic control has been well documented. Supplemented at 10 g/d for 8 wk, FOS-enriched inulin was shown to reduce serum IL-4, IL-12, and INF-γ in one study (127), and reduce plasma IL-6, TNF-α, and LPS in another (128), both in overweight women with T2DM. Inulin supplementation (10 g/d) for 8 wk was also shown to decrease fasting concentrations of high-sensitivity CRP (-2.7 compared with -1.1 ng/mL), TNF-α (-3.0 compared with -1.4 pg/mL), and LPS (-5.4 compared with +0.1 EU/mL) in overweight women with T2DM (122). Additionally, in a randomized, controlled, parallel trial, women with T2DM who consumed resistant dextrin (10 g/d) for 8 wk had reduced concentrations of plasma IL-6, TNF-α, and malondialdehyde, as well as reduced serum endotoxin, compared with those in the placebo group (129).

Healthy subjects

In cases of chronic inflammation, as with IBD and many metabolic diseases, reducing proinflammatory metabolites is clearly a beneficial endpoint. However, is it healthy to reduce inflammatory markers in a population that does not have elevated inflammation? This also raises the question: should healthy populations be used to determine whether fermentable fiber results in anti-inflammatory responses? Many clinical trials have investigated the effects of fermentable fibers on GI health and inflammation in healthy human populations, and the results are more mixed. Inulin and FOS are among the many fibers studied. Inulin supplementation at 20 g/d for 3 wk has been shown to increase fecal *Lactobacillus* relative abundance and decrease both fecal ammonia concentrations and β-glucuronidase activity, which have both been positively associated with increased risk of CRC (130). Inulin also was observed to improve measures of GI permeability (lactulose:mannitol excretion ratio, lactulose recovery, serum zonulin) compared with a control group when supplemented at 11 g/d for 5 wk (131). When given a combination of inulin (3 g/d) and XOS (1 g/d) for 4 wk, healthy participants exhibited an increase in fecal SCFAs, decreased circulating LPS, and decreased LPS-induced IL-1β expression. XOS alone (5 g/d) did not produce these effects (132). However, a FOS/inulin blend did not alter immune cell populations, activation, or proliferation when consumed by healthy individuals for 8 wk at 8 g/d (133).

Arabinoxylanoligosaccharides (AXOS) and GOSs have been shown to improve markers of GI health and inflammation in healthy individuals, particularly in low doses. AXOS supplemented at only 2.14 g/d for 3 wk increased fecal SCFAs, especially butyrate, bifidobacteria relative abundance, and stool frequency (134). Wheat bran extract (WBE) contains ~79% AXOS and up to 15% β-glucans. A dose of 10 g WBE (8 g/d AXOS) increased fecal bifidobacteria relative abundance and SCFA concentrations, with a corresponding decrease in fecal pH. Urinary *p*-cresol was also reduced following WBE supplementation, indicating a reduction in protein fermentation (135). WBE has also been shown to reduce protein fermentation compared with a maltodextrin placebo when supplemented at 10 g/d for 3 wk in healthy participants (104). In contrast, another study that gave healthy participants 5 g/d AXOS, as WBE, for 3 wk observed no changes in fecal SCFAs or pH. However, they observed a decrease in fecal BCFA, supporting previous results of reduced protein fermentation (136). In healthy, elderly individuals, supplementation with 5.5 g GOS/d for 10 wk resulted in an increase in relative abundance of bifidobacteria, which was correlated with increased lactic

acid in fecal water. Additionally, stimulated peripheral blood mononuclear cells obtained at the end of the study showed a greater production of IL-10 (114 compared with 62 pg/mL) and IL-8 (4140 compared with 3171 pg/mL) and a lower production of IL-1β (954 compared with 1281 pg/mL) in the GOS group compared with the placebo group. Although serum CRP concentrations were higher following GOS treatment than with placebo, these concentrations remained substantially lower than those associated with negative effects (137).

Summary

Consumption of highly fermentable fibers have been shown to improve biomarkers of GI health and systemic inflammation as well as endoscopic and histologic scores of GI health in individuals with IBD, metabolic disease, overweight, and obesity. For patients with IBD, the use of SCFA enemas has been shown to be beneficial in attenuating symptoms and prolonging remission. The data in healthy participants, although large, are less conclusive. However, the ability of fermentable fibers to modulate inflammation is arguably better assessed in populations that have chronic, elevated systemic inflammation rather than healthy populations who may not stand to benefit from decreased immune activity.

Conclusions

Fermentation of dietary NDCs produce SCFAs that curb the glycemic response, promote satiety and weight loss, increase mineral absorption, reduce biomarkers of chronic systemic inflammation, and improve intestinal health and integrity. **Table 2** provides a summary of key findings for each population discussed in this review. Although production of SCFAs by NDC fermentation is not itself a physiologic endpoint, it has become increasingly evident that many of the clinical effects elicited by fermentable NDCs are directly mediated by fermentative end-products, such as SCFAs. Due to the obvious systemic physiologic importance of fermentation, we argue that the degree of fermentability of an NDC, rather than the outcome of a clinical trial, may be sufficient in classifying it as a dietary fiber.

Acknowledgments

All authors have read and approved the final manuscript.

References

1. United States Food and Drug Administration. Food labeling: revision of the nutrition and supplement facts labels (21 CFR part 101). Washington (DC): Food and Drug Administration, Health and Human Services; 2016. pp. 33742–999.
2. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. Gut Microbes 2017;8:172–84.
3. United States Food and Drug Administration. The declaration of certain isolated or synthetic non-digestible carbohydrates as dietary fiber on nutrition and supplement facts labels; guidance for industry; availability. Washington (DC): Food and Drug Administration, Health and Human Services; 2018. pp. 1–8.
4. United States Food and Drug Administration. Scientific evaluation of the evidence on the beneficial physiological effects of isolated or synthetic non-digestible carbohydrates submitted as a citizen petition (21 CFR 10.30): guidance for industry. College Park (MD): Food and Drug Administration, Health and Human Services; 2018. pp. 1–16.
5. U.S. Department of Health and Human Services, U.S. Department of Agriculture. 2015–2020 dietary guidelines for Americans. 8th edition. 2015.
6. Dietary Guidelines Advisory Committee. Scientific report of the 2015 Dietary Guidelines Advisory Committee to the Secretary of Health and Human Services and the Secretary of Agriculture. Washington (DC); 2015.
7. Burkitt DP. Some diseases characteristic of modern western civilization. Br Med J 1973;1:274–8.
8. Williams BA, Grant LJ, Gidley MJ, Mikkelsen D. Gut fermentation of dietary fibres: physico-chemistry of plant cell walls and implications for health. Int J Mol Sci 2017;18: 2203.
9. Verbeke KA, Boobis AR, Chiodini A, Edwards CA, Franck A, Kleerebezem M, Nauta A, Raes J, van Tol EAF, Tuohy KM. Towards microbial fermentation metabolites as markers for health benefits of prebiotics. Nutr Res Rev 2015;28:42–66.
10. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 2016;165:1332–45.
11. Wong JMW, de Souza R, Kendall CWC, Emam A, Jenkins DJA. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol 2006;40:235–43.
12. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev 2001;81:1031–64.
13. Lombard V, Golaconda Ramulu H, Drula E, Coutinho PM, Henrissat B. The carbohydrate-active enzymes database (CAZy) in 2013. Nucleic Acids Res 2014;42:490–5.
14. Jenkins DJA, Kendall CWC, Vuksan V. Inulin, oligofructose and intestinal function. J Nutr 1999;129:1431S–3S.
15. Hernot DC, Boileau TW, Bauer LL, Middelbos IS, Murphy MR, Swanson KS, Fahey GC. In vitro fermentation profiles, gas production rates, and microbiota modulation as affected by certain fructans, galactooligosaccharides, and polydextrose. J Agric Food Chem 2009;57:1354–61.
16. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud D-J, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res 2013;54:2325–40.
17. Halestrap AP, Wilson MC. The monocarboxylate transporter family—role and regulation. IUBMB Life 2012;64:109–19.
18. Bergman EN. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. Physiol Rev 1990;70: 567–90.
19. Kasubuchi M, Hasegawa S, Hiramatsu T, Ichimura A, Kimura I. Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. Nutrients 2015;7:2839–49.
20. Roediger WEW. Utilization of nutrients by isolated epithelial cells of the rat colon. Gastroenterology 1982;83:424–9.
21. Scholz-Ahrens KE, Ade P, Marten B, Weber P, Timm W, Açil Y, Glüer C-C, Schrezenmeir J. Prebiotics, probiotics, and synbiotics affect mineral absorption, bone mineral content, and bone structure. J Nutr 2007;137:838S–46S.
22. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe 2015;17: 565–76.
23. Bourassa MW, Alim I, Bultman SJ, Ratan RR. Butyrate, neuroepigenetics and the gut microbiome: can a high fiber diet improve brain health? Neurosci Lett 2016;625:56–63.
24. Meyer D. Health benefits of prebiotic fibers. Advances in food and nutrition research. 1st edition. Elsevier; 2015. pp. 47–91.
25. Rumpagaporn P, Reuhs BL, Kaur A, Patterson JA, Keshavarzian A, Hamaker BR. Structural features of soluble cereal arabinoxylan fibers

associated with a slow rate of in vitro fermentation by human fecal microbiota. Carbohydr Polym 2015;130:191–7.
26. Hughes SA, Shewry PR, Li L, Gibson GR, Sanz ML, Rastall RA. In vitro fermentation by human fecal microflora of wheat arabinoxylans. J Agric Food Chem 2007;55:4589–95.
27. Vernazza CL, Gibson GR, Rastall RA. In vitro fermentation of chitosan derivatives by mixed cultures of human faecal bacteria. Carbohydr Polym 2005;60:539–45.
28. Kaur A, Rose DJ, Rumpagaporn P, Patterson JA, Hamaker BR. In vitro batch fecal fermentation comparison of gas and short-chain fatty acid production using "slowly fermentable" dietary fibers. J Food Sci 2011;76:137–42.
29. Bourquin LD, Titgemeyer EC, Fahey GC. Fermentation of various dietary fiber sources by human fecal bacteria. Nutr Res 1996;16: 1119–31.
30. Noack J, Timm D, Hospattankar A, Slavin J. Fermentation profiles of wheat dextrin, inulin and partially hydrolyzed guar gum using an in vitro digestion pretreatment and in vitro batch fermentation system model. Nutrients 2013;5:1500–10.
31. Carlson J, Hospattankar A, Deng P, Swanson K, Slavin J. Prebiotic effects and fermentation kinetics of wheat dextrin and partially hydrolyzed guar gum in an in vitro batch fermentation system. Foods 2015;4:349–58.
32. Campbell JM, Fahey GC. Psyllium and methylcellulose fermentation properties in relation to insoluble and soluble fiber standards. Nutr Res 1997;17:619–29.
33. Maathuis A, Hoffman A, Evans A, Sanders L, Venema K. The effect of the undigested fraction of maize products on the activity and composition of the microbiota determined in a dynamic in vitro model of the human proximal large intestine. J Am Coll Nutr 2009;28: 657–66.
34. Müller M, Canfora EE, Blaak EE. Gastrointestinal transit time, glucose homeostasis and metabolic health: modulation by dietary fibers. Nutrients 2018;10:E275.
35. Fletcher JA, Perfield JW, Thyfault JP, Rector RS. The second meal effect and its influence on glycemia. J Nutr Disord Ther 2012;2: 1000108.
36. Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. Adv Immunol 2014;121:91–119.
37. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas M-E. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med 2016;8:1–12.
38. Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, Fu H, Xue X, Lu C, Ma J, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science 2018;359:1151–6.
39. Guess ND, Dornhorst A, Oliver N, Frost GS. A randomised crossover trial: the effect of inulin on glucose homeostasis in subtypes of prediabetes. Ann Nutr Metab 2016;68:26–34.
40. Guess ND, Dornhorst A, Oliver N, Bell JD, Thomas EL, Frost GS. A randomized controlled trial: the effect of inulin on weight management and ectopic fat in subjects with prediabetes. Nutr Metab 2015; 12:36.
41. Mateos-Aparicio I, Mengíbar M, Heras A. Effect of chito-oligosaccharides over human faecal microbiota during fermentation in batch cultures. Carbohydr Polym 2016;137:617–24.
42. Kim HJ, Ahn HY, Kwak JH, Shin DY, Kwon Y-I, Oh C-G, Lee JH. The effects of chitosan oligosaccharide (GO2KA1) supplementation on glucose control in subjects with prediabetes. Food Funct 2014;5: 2662–9.
43. Kwak JH, Paik JK, Kim HI, Kim OY, Shin DY, Kim HJ, Lee JH, Lee JH. Dietary treatment with rice containing resistant starch improves markers of endothelial function with reduction of postprandial blood glucose and oxidative stress in patients with prediabetes or newly diagnosed type 2 diabetes. Atherosclerosis 2012;224:457–64.
44. Freeland KR, Wilson C, Wolever TMS. Adaptation of colonic fermentation and glucagon-like peptide-1 secretion with increased wheat fibre intake for 1 year in hyperinsulinaemic human subjects. Br J Nutr 2010;103:82–90.
45. Hartvigsen ML, Lærke HN, Overgaard A, Holst JJ, Bach Knudsen KE, Hermansen K. Postprandial effects of test meals including concentrated arabinoxylan and whole grain rye in subjects with the metabolic syndrome: a randomised study. Eur J Clin Nutr 2014;68:567–74.
46. Savastano DM, Hodge RJ, Nunez DJ, Walker A, Kapikian R. Effect of two dietary fibers on satiety and glycemic parameters: a randomized, double-blind, placebo-controlled, exploratory study. Nutr J 2014;13:45.
47. Daud NM, Ismail NA, Thomas EL, Fitzpatrick JA, Bell JD, Swann JR, Costabile A, Childs CE, Pedersen C, Goldstone AP, et al. The impact of oligofructose on stimulation of gut hormones, appetite regulation and adiposity. Obesity 2014;22:1430–8.
48. Morel FB, Dai Q, Ni J, Thomas D, Parnet P, Fanca-Berthon P. Galacto-oligosaccharides dose-dependently reduce appetite and decrease inflammation in overweight adults. J Nutr 2015;145: 2052–9.
49. Chambers ES, Viardot A, Psichas A, Morrison DJ, Murphy KG, Zac-Varghese SEK, MacDougall K, Preston T, Tedford C, Finlayson GS, et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. Gut 2015;64:1744–54.
50. Bodinham CL, Smith L, Wright J, Frost GS, Robertson MD. Dietary fibre improves first-phase insulin secretion in overweight individuals. PLoS One 2012;7:1–6.
51. Lafond DW, Greaves KA, Maki KC, Leidy HJ, Romsos DR. Effects of two dietary fibers as part of ready-to-eat cereal (RTEC) breakfasts on perceived appetite and gut hormones in overweight women. Nutrients 2015;7:1245–66.
52. Li S, Guerin-Deremaux L, Pochat M, Wils D, Reifer C, Miller LE. NUTRIOSE dietary fiber supplementation improves insulin resistance and determinants of metabolic syndrome in overweight men: a double-blind, randomized, placebo-controlled study. Appl Physiol Nutr Metab 2010;35:773–82.
53. Rahat-Rozenbloom S, Fernandes J, Cheng J, Gloor GB, Wolever TMS. The acute effects of inulin and resistant starch on postprandial serum short-chain fatty acids and second-meal glycemic response in lean and overweight humans. Eur J Clin Nutr 2017;71:227–33.
54. Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D, De Backer F, Neyrinck AM, Delzenne NM. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. Am J Clin Nutr 2009;90:1236–43.
55. Tarini J, Wolever TMS. The fermentable fibre inulin increases postprandial serum short-chain fatty acids and reduces free-fatty acids and ghrelin in healthy subjects. Appl Physiol Nutr Metab 2010;35:9–16.
56. Verhoef SPM, Meyer D, Westerterp KR. Effects of oligofructose on appetite profile, glucagon-like peptide 1 and peptide YY3-36 concentrations and energy intake. Br J Nutr 2011;106:1757–62.
57. Morris C, Lynn A, Neveux C, Hall AC, Morris GA. Impact of bread making on fructan chain integrity and effect of fructan enriched breads on breath hydrogen, satiety, energy intake, PYY and ghrelin. Food Funct 2015;6:2561–7.
58. Lu ZX, Walker KZ, Muir JG, Mascara T, O'Dea K. Arabinoxylan fiber, a byproduct of wheat flour processing, reduces the postprandial glucose response in normoglycemic subjects. Am J Clin Nutr 2000;71: 1123–8.
59. Wanders AJ, Mars M, Borgonjen-Van Den Berg KJ, De Graaf C, Feskens EJM. Satiety and energy intake after single and repeated exposure to gel-forming dietary fiber: post-ingestive effects. Int J Obes 2014;38:794–800.
60. Robertson MD, Currie JM, Morgan LM, Jewell DP, Frayn KN. Prior short-term consumption of resistant starch enhances postprandial insulin sensitivity in healthy subjects. Diabetologia 2003;46: 659–65.

61. Leclère C, Champ M, Boillot J, Guille G, Lecannu G, Molis C, Bornet F, Krempf M, Delort-Laval J, Galmiche J. Role of viscous response after guar gums in lowering the glycemic response after a solid meal. Am J Clin Nutr 1994;59:914–21.
62. Jenkins DJ, Wolever TM, Taylor RH, Barker HM, Fielden H, Jenkins AL. Effect of guar crispbread with cereal products and leguminous seeds on blood glucose concentrations of diabetics. Br Med J 1980;281:1248–50.
63. Dall'Alba V, Silva FM, Antonio JP, Steemburgo T, Royer CP, Almeida JC, Gross JL, Azevedo MJ. Improvement of the metabolic syndrome profile by soluble fibre—guar gum—in patients with type 2 diabetes: a randomised clinical trial. Br J Nutr 2013;110:1601–10.
64. Harrold J, Breslin L, Walsh J, Halford J, Pelkman C. Satiety effects of a whole-grain fibre composite ingredient: reduced food intake and appetite ratings. Food Funct 2014;5:2574–81.
65. Luhovyy BL, Mollard RC, Yurchenko S, Nunez MF, Berengut S, Liu TT, Smith CE, Pelkman CL, Anderson GH. The effects of whole grain high-amylose maize flour as a source of resistant starch on blood glucose, satiety, and food intake in young men. J Food Sci 2014;79: H2550–6.
66. Bodinham CL, Al-Mana NM, Smith L, Robertson MD. Endogenous plasma glucagon-like peptide-1 following acute dietary fibre consumption. Br J Nutr 2013;110:1429–33.
67. Rao TP, Hayakawa M, Minami T, Ishihara N, Kapoor MP, Ohkubo T, Juneja LR, Wakabayashi K. Post-meal perceivable satiety and subsequent energy intake with intake of partially hydrolysed guar gum. Br J Nutr 2015;113:1489–98.
68. Wanders AJ, Feskens EJM, Jonathan MC, Schols HA, de Graaf C, Mars M. Pectin is not pectin: a randomized trial on the effect of different physicochemical properties of dietary fiber on appetite and energy intake. Physiol Behav 2014;128:212–9.
69. Lobley GE, Holtrop G, Bremner DM, Calder AG, Milne E, Johnstone AM. Impact of short term consumption of diets high in either non-starch polysaccharides or resistant starch in comparison with moderate weight loss on indices of insulin sensitivity in subjects with metabolic syndrome. Nutrients 2013;5: 2144–72.
70. Jenkins AL, Jenkins DJA, Wolever TMS, Rogovik AL, Jovanovski E, Božikov V, Rahelić D, Vuksan V. Comparable postprandial glucose reductions with viscous fiber blend enriched biscuits in healthy subjects and patients with diabetes mellitus: acute randomized controlled clinical trial. Croat Med J 2008;49: 772–82.
71. Brockman DA, Chen X, Gallaher DD. High-viscosity dietary fibers reduce adiposity and decrease hepatic steatosis in rats fed a high-fat diet. J Nutr 2014;144:1415–22.
72. Scholz-Ahrens KE, Schrezenmeir J. Inulin, oligofructose and mineral metabolism—experimental data and mechanism. Br J Nutr 2002;87:S179.
73. Cauley JA. Bone health after menopause. Curr Opin Endocrinol Diabetes Obes 2015;22:490–4.
74. Tahiri M, Tressol JC, Arnaud J, Bornet FRJ, Bouteloup-Demange C, Feillet-Coudray C, Brandolini M, Ducros V, Pépin D, Brouns F, et al. Effect of short-chain fructooligosaccharides on intestinal calcium absorption and calcium status in postmenopausal women: a stable-isotope study. Am J Clin Nutr 2003;77:449–57.
75. Slevin MM, Allsopp PJ, Magee PJ, Bonham MP, Naughton VR, Strain JJ, Duffy ME, Wallace JM, McSorley EM. Supplementation with calcium and short-chain fructo-oligosaccharides affects markers of bone turnover but not bone mineral density in postmenopausal women. J Nutr 2014;144:297–304.
76. Holloway L, Moynihan S, Abrams SA, Kent K, Hsu AR, Friedlander AL. Effects of oligofructose-enriched inulin on intestinal absorption of calcium and magnesium and bone turnover markers in postmenopausal women. Br J Nutr 2007;97:365–72.
77. Jakeman SA, Henry CN, Martin BR, McCabe GP, McCabe LD, Jackson GS, Peacock M, Weaver CM. Soluble corn fiber increases bone calcium retention in postmenopausal women in a dose-dependent manner: a randomized crossover trial. Am J Clin Nutr 2016;104: 837–43.
78. Armas LAG, Rafferty K, Hospattankar A, Abrams SA, Heaney RP. Chronic dietary fiber supplementation with wheat dextrin does not inhibit calcium and magnesium absorption in premenopausal and postmenopausal women. J Int Med Res 2011;39: 1824–33.
79. van den Heuvel EGHM, Muijs T, Brouns F, Hendriks HFJ. Short-chain fructo-oligosaccharides improve magnesium absorption in adolescent girls with a low calcium intake. Nutr Res 2009;29: 229–37.
80. Paganini D, Uyoga MA, Cercamondi CI, Moretti D, Mwasi E, Schwab C, Bechtler S, Mutuku FM, Lacroix C, Karanja S, et al. Consumption of galacto-oligosaccharides increases iron absorption from a micronutrient powder containing ferrous fumarate and sodium iron EDTA: a stable isotope study in Kenyan infants. Am J Clin Nutr 2017;106:1020–31.
81. Sanwalka NJ, Khadilkar AV, Chiplonkar SA, Khadilkar V., Mughal MZ. Galacto-fructo-oligosaccharide fortification of fermented non-dairy snack enhances calcium absorption in healthy adolescent girls. Int J Food Sci Nutr 2012;63:343–52.
82. van den Heuvel EGHM, Muys T, van Dokkum W, Schaafsma G. Oligofructose stimulates calcium absorption in adolescents. Am J Clin Nutr 1999;69:544–8.
83. Abrams SA, Griffin IJ, Hawthorne KM, Liang L, Gunn SK, Darlington G, Ellis KJ. A combination of prebiotic short- and long-chain inulin-type fructans enhances calcium absorption and bone mineralization in young adolescents. Am J Clin Nutr 2005;82:471–6.
84. Abrams SA, Griffin IJ, Hawthorne KM. Young adolescents who respond to an inulin-type fructan substantially increase total absorbed calcium and daily calcium accretion to the skeleton. J Nutr 2007;137:2524S–6S.
85. Griffin IJ, Davila PM, Abrams SA. Non-digestible oligosaccharides and calcium absorption in girls with adequate calcium intakes. Br J Nutr 2002;87(Suppl 2):S187–91.
86. Han K, Kobayashi Y, Nakamura Y, Shimada K, Aritsuka T, Ohba K, Morita T, Fukushima M. Comparison of the effects of longer chain inulins with different degrees of polymerization on colonic fermentation in a mixed culture of swine fecal bacteria. J Nutr Sci Vitaminol 2014;60:206–12.
87. Martin BR, Braun MM, Wigertz K, Bryant R, Zhao Y, Lee WH, Kempa-Steczko A, Weaver CM. Fructo-oligosaccharides and calcium absorption and retention in adolescent girls. J Am Coll Nutr 2010;29:382–6.
88. Whisner CM, Martin BR, Nakatsu CH, McCabe GP, McCabe LD, Peacock M, Weaver CM. Soluble maize fibre affects short-term calcium absorption in adolescent boys and girls: a randomised controlled trial using dual stable isotopic tracers. Br J Nutr 2014;112: 446–56.
89. Whisner CM, Martin BR, Nakatsu CH, Story JA, MacDonald-Clarke CJ, McCabe LD, McCabe GP, Weaver CM. Soluble corn fiber increases calcium absorption associated with shifts in the gut microbiome: a randomized dose-response trial in free-living pubertal females. J Nutr 2016;146:1298–306.
90. Coudray C, Bellanger J, Castiglia-Delavaud C, Remesy C, Vermorel M, Rayssignuier Y. Effect of soluble or partly soluble dietary fibres supplementation on absorption and balance of calcium, magnesium, iron and zinc in healthy young men. Eur J Clin Nutr 1997;51:375–80.
91. van den Heuvel EGHM, Schaafsma G, Muys T, van Dokkum W. Nondigestible oligosaccharides do not interfere with calcium and nonheme-iron absorption in young, healthy men. Am J Clin Nutr 1998;67:445–51.
92. Petry N, Egli I, Chassard C, Lacroix C, Hurrell R. Inulin modifies the bifidobacteria population, fecal lactate concentration, and fecal pH but does not influence iron absorption in women with low iron status. Am J Clin Nutr 2012;96:325–31.
93. Weinborn V, Valenzuela C, Olivares M, Arredondo M, Weill R, Pizarro F. Prebiotics increase heme iron bioavailability and do not

affect non-heme iron bioavailability in humans. Food Funct 2017;8: 1994–9.
94. Vermorel M, Coudray C, Wils D, Sinaud S, Tressol JC, Montaurier C, Vernet J, Brandolini M, Bouteloup-Demange C, Rayssiguier Y. Energy value of a low-digestible carbohydrate, NUTRIOSE® FB, and its impact on magnesium, calcium and zinc apparent absorption and retention in healthy young men. Eur J Nutr 2004;43:344–52.
95. Cummings JH, Southgate DA, Branch WJ, Wiggins HS, Houston H, Jenkins DJA, Jivraj T, Hill MJ. The digestion of pectin in the human gut and its effect on calcium absorption and large bowel function. Br J Nutr 1979;41:477–85.
96. Swanson KS, Grieshop CM, Clapper GM, Shields RG, Belay T, Merchen NR, Fahey GC. Fruit and vegetable fiber fermentation by gut microflora from canines. J Anim Sci 2001;79:919–26.
97. Marteau P, Flourié B, Cherbut C, Corrèze JL, Pellier P, Seylaz J, Rambaud JC. Digestibility and bulking effect of ispaghula husks in healthy humans. Gut 1994;35:1747–52.
98. Heaney RP, Weaver CM. Effect of psyllium on absorption of co-ingested calcium. J Am Geriatr Soc 1995;43:261–3.
99. Balasubramanian R, Johnson EJ, Marlett JA. Effect of wheat bran on bowel function and fecal calcium in older adults. J Am Coll Nutr 1987;6:199–208.
100. O'Brien K, Allen L. High fiber diets slow bone turnover in young men but have no effect on efficiency of intestinal calcium absorption. J Nutr 1993;123:2122–8.
101. van Dokkum W, Wesstra A, Schippers FA. Physiological effects of fibre-rich types of bread 1. The effect of dietary fibre from bread on the mineral balance of young men. Br J Nutr 1982;47:451–60.
102. Andersson H, Navert B, Bingham SA, Englyst HN, Cummings JH. The effects of breads containing similar amounts of phytate but different amounts of wheat bran on calcium, zinc and iron balance in man. Br J Nutr 1983;50:503–10.
103. Greger JL. Nondigestible carbohydrates and mineral bioavailability. J Nutr 1999;129:1434S–5S.
104. Windey K, De Preter V, Huys G, Broekaert WF, Delcour JA, Louat T, Herman J, Verbeke K. Wheat bran extract alters colonic fermentation and microbial composition, but does not affect faecal water toxicity: a randomised controlled trial in healthy subjects. Br J Nutr 2015;113:225–38.
105. Macfarlane GT, Macfarlane S. Bacteria, colonic fermentation, and gastrointestinal health. J AOAC Int 2012;95:50–9.
106. Nyangale EP, Mottram DS, Gibson GR. Gut microbial activity, implications for health and disease: the potential role of metabolite analysis. J Proteome Res 2012;11:5573–85.
107. Jennis M, Cavanaugh CR, Leo GC, Mabus JR, Lenhard J, Hornby PJ. Microbiota-derived tryptophan indoles increase after gastric bypass surgery and reduce intestinal permeability in vitro and in vivo. Neurogastroenterol Motil 2017;30:e13178.
108. Roager HM, Licht TR. Microbial tryptophan catabolites in health and disease. Nat Commun 2018;9:3294.
109. Derikx LAAP, Dieleman LA, Hoentjen F. Probiotics and prebiotics in ulcerative colitis. Best Pract Res Clin Gastroenterol 2016;30:55–71.
110. Wells JM, Brummer RJ, Derrien M, MacDonald TT, Troost F, Cani PD, Theodorou V, Dekker J, Méheust A, de Vos WM, et al. Homeostasis of the gut barrier and potential biomarkers. Am J Physiol Gastrointest Liver Physiol 2017;312:G171–93.
111. Scheppach W, Sommer H, Kirchner T, Paganelli GM, Bartram P, Christl S, Richter F, Dusel G, Kasper H. Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. Gastroenterology 1992;103:51–6.
112. Lührs H, Gerke T, Müller J, Melcher R, Schauber J, Boxberger F, Scheppach W, Menzel T. Butyrate inhibits NF-κB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol 2002;37:458–66.
113. Vernia P, Marcheggiano A, Caprilli R, Frieri G, Corraos G, Valpianit D, Di Paolo MC, Paoluzi P, Torsoli A. Short-chain fatty acid topical treatment in distal ulcerative colitis. Aliment Pharmacol Ther 1995;9:309–13.
114. Scheppach W. Treatment of distal ulcerative colitis with short-chain fatty acid enemas. A placebo-controlled trial. German-Austrian SCFA Study Group. Dig Dis Sci 1996;41:2254–9.
115. Benjamin JL, Hedin CRH, Koutsoumpas A, Ng SC, McCarthy NE, Hart AL, Kamm MA, Sanderson JD, Knight SC, Forbes A, et al. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. Gut 2011;60: 923–9.
116. Mitsuyama K, Saiki T, Kanauchi O, Iwanaga T, Tomiyasu N, Nishiyama T, Tateishi H, Shirachi A, Ide M, Suzuki A, et al. Treatment of ulcerative colitis with germinated barley foodstuff feeding: a pilot study. Aliment Pharmacol Ther 1998;12:1225–30.
117. Faghfoori Z, Navai L, Shakerhosseini R, Somi MH, Nikniaz Z, Norouzi MF. Effects of an oral supplementation of germinated barley foodstuff on serum tumour necrosis factor-α, interleukin-6 and -8 in patients with ulcerative colitis. Ann Clin Biochem 2011;48:233–7.
118. Faghfoori Z, Shakerhosseini R, Navai L, Somi MH, Nikniaz Z, Abadi A. Effects of an oral supplementation of germinated barley foodstuff on serum CRP level and clinical signs in patients with ulcerative colitis. Heal Promot Perspect 2014;4:116–21.
119. Hanai H, Kanauchi O, Mitsuyama K, Andoh A, Takeuchi K, Takayuki I, Araki Y, Fujiyama Y, Toyonaga A, Sata M, et al. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. Int J Mol Med 2004;13:643–7.
120. Zhan Y, Zhan Y, Dai S. Is a low FODMAP diet beneficial for patients with inflammatory bowel disease? A meta-analysis and systematic review. Clin Nutr 2018;37:123–9.
121. Hermsdorff HHM, Zulet MÁ, Abete I, Martínez JA. A legume-based hypocaloric diet reduces proinflammatory status and improves metabolic features in overweight/obese subjects. Eur J Nutr 2011;50:61–9.
122. Dehghan P, Gargari BP, Jafar-Abadi MA, Aliasgharzadeh A. Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial. Int J Food Sci Nutr 2014;65:117–23.
123. Kim JY, Kwon HY, Kim KS, Kim MK, Kwon O. Postprandial glucose and NF-κB responses are regulated differently by monounsaturated fatty acid and dietary fiber in impaired fasting glucose subjects. J Med Food 2013;16:1168–71.
124. Mallillin AC, Trinidad TP, Raterta R, Dagbay K, Loyola AS. Dietary fibre and fermentability characteristics of root crops and legumes. Br J Nutr 2008;100:485–8.
125. Reverri EJ, Randolph JM, Steinberg FM, Tissa Kappagoda C, Edirisinghe I, Burton-Freeman BM. Black beans, fiber, and antioxidant capacity pilot study: examination of whole foods vs. functional components on postprandial metabolic, oxidative stress, and inflammation in adults with metabolic syndrome. Nutrients 2015;7:6139–54.
126. Vulevic J, Juric A, Tzortzis G, Gibson GR. A mixture of trans-galactooligosaccharides reduces markers of metabolic syndrome and modulates the fecal microbiota and immune function of overweight adults. J Nutr 2013;143:324–31.
127. Dehghan P, Farhangi MA, Tavakoli F, Aliasgarzadeh A, Akbari AM. Impact of prebiotic supplementation on T-cell subsets and their related cytokines, anthropometric features and blood pressure in patients with type 2 diabetes mellitus: a randomized placebo-controlled trial. Complement Ther Med 2016;24:96–102.
128. Dehghan P, Gargari BP, Asghari-Jafarabadi M. Oligofructose-enriched inulin improves some inflammatory markers and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized controlled clinical trial. Nutrition 2014;30:418–23.
129. Aliasgharzadeh A, Dehghan P, Gargari BP, Asghari-Jafarabadi M. Resistant dextrin, as a prebiotic, improves insulin resistance and inflammation in women with type 2 diabetes: a randomised controlled clinical trial. Br J Nutr 2015;113:321–30.
130. Slavin J, Feirtag J. Chicory inulin does not increase stool weight or speed up intestinal transit time in healthy male subjects. Food Funct 2011;2:72–7.

131. Russo F, Linsalata M, Clemente C, Chiloiro M, Orlando A, Marconi E, Chimienti G, Riezzo G. Inulin-enriched pasta improves intestinal permeability and modifies the circulating levels of zonulin and glucagon-like peptide 2 in healthy young volunteers. Nutr Res 2012;32:940–6.
132. Lecerf J-M, Dépeint F, Clerc E, Dugenet Y, Niamba CN, Rhazi L, Cayzeele A, Abdelnour G, Jaruga A, Younes H, et al. Xylo-oligosaccharide (XOS) in combination with inulin modulates both the intestinal environment and immune status in healthy subjects, while XOS alone only shows prebiotic properties. Br J Nutr 2012;108:1847–58.
133. Lomax AR, Cheung LVY, Tuohy KM, Noakes PS, Miles EA, Calder PC. β2-1 Fructans have a bifidogenic effect in healthy middle-aged human subjects but do not alter immune responses examined in the absence of an in vivo immune challenge: results from a randomised controlled trial. Br J Nutr 2012;108:1818–28.
134. Damen B, Cloetens L, Broekaert WF, Francois I, Lescroart O, Trogh I, Arnaut F, Welling GW, Wijffels J, Delcour JA, et al. Consumption of breads containing in situ-produced arabinoxylan oligosaccharides alters gastrointestinal effects in healthy volunteers. J Nutr 2012;142:470–7.
135. François IEJA, Lescroart O, Veraverbeke WS, Marzorati M, Possemiers S, Evenepoel P, Hamer H, Houben E, Windey K, Welling GW, et al. Effects of a wheat bran extract containing arabinoxylan oligosaccharides on gastrointestinal health parameters in healthy adult human volunteers: a double-blind, randomised, placebo-controlled, cross-over trial. Br J Nutr 2012;108: 2229–42.
136. François IEJA, Lescroart O, Veraverbeke WS, Marzorati M, Possemiers S, Hamer H, Windey K, Welling GW, Delcour JA, Courtin CM, et al. Effects of wheat bran extract containing arabinoxylan oligosaccharides on gastrointestinal parameters in healthy preadolescent children. J Pediatr Gastroenterol Nutr 2014;58: 647–53.
137. Vulevic J, Juric A, Walton GE, Claus SP, Tzortzis G, Toward RE, Gibson GR. Influence of galacto-oligosaccharide mixture (B-GOS) on gut microbiota, immune parameters and metabonomics in elderly persons. Br J Nutr 2015;114:586–95.