Lead Article

Current explorations of nutrition and the gut microbiome: a comprehensive evaluation of the review literature

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Context: *The ability to measure the gut microbiome led to a surge in understanding and knowledge of its role in health and disease. The diet is a source of fuel for and influencer of composition of the microbiome.* ***Objective:*** *To assess the understanding of the interactions between nutrition and the gut microbiome in healthy adults.* ***Data Sources:*** *PubMed and Google Scholar searches were conducted in March and August 2018 and were limited to the following: English, 2010–2018, healthy adults, and reviews.* ***Data Extraction:*** *A total of 86 articles were independently screened for duplicates and relevance, based on preidentified inclusion criteria.* ***Data Analysis:*** *Research has focused on dietary fiber – microbiota fuel. The benefits of fiber center on short-chain fatty acids, which are required by colonocytes, improve absorption, and reduce intestinal transit time. Contrastingly, protein promotes microbial protein metabolism and potentially harmful by-products that can stagnate in the gut. The microbiota utilize and produce micronutrients; the bidirectional relationship between micronutrition and the gut microbiome is emerging.* ***Conclusions:*** *Nutrition has profound effects on microbial composition, in turn affecting wide-ranging metabolic, hormonal, and neurological processes. There is no consensus on what defines a "healthy" gut microbiome. Future research must consider individual responses to diet.*

INTRODUCTION

In 1683, while using a microscope to observe the plaque that had been scraped from his own teeth, Antonie van Leeuwenhoek reported that "there were many very little living *animalcules*, very prettily a-moving."[1] Not only was Leeuwenhoek first to observe and describe microorganisms scientifically, he also established that humans are hosts to large numbers of diverse microorganisms. Nearly 200 years later, in 1857, Louis Pasteur reported that "the chemical act of fermentation is essentially a phenomenon correlative with a vital act" after discovering that microorganisms were responsible for the basic mechanism of fermentation.[2] Towards the end of the 19th century, Pasteur and Robert Koch demonstrated conclusively that microorganisms were agents of disease, and in doing so, forged the acceptance of the "germ theory" for infectious disease. These events stigmatized the public's perception of microorganisms, and, throughout much of the 20th century, microorganisms were largely seen as adversarial due to their association with disease and food spoilage. It would take another century before technology ushered in the next transformation in our understanding of the important roles that microorganisms play in our daily life.

In the last decade, advances in DNA sequencing technologies have allowed this technology to become ubiquitous in research laboratories around the world. It

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was through the use of next-generation sequencing (NGS) technologies that scientists, for the first time, were able to measure and describe the vast microbial ecosystems that live in and on our bodies (dubbed the human microbiome). NGS-based measurements have revealed the presence of 1000's of diverse species of prokaryotes, archaea, eukaryotes, and viruses that collectively make-up our human microbiome. Further, a typical human being is made-up of more microbial cells than human cells.[3] The human microbiome is phylogenetically diverse, and this diversity gives rise to an immense metabolic potential; perhaps best described by the number of microbial genes contained within the human microbiome. While a human genome contains on the order of 20,000 genes, a human microbiome collectively contains on the order of 3 million (non-redundant) genes.[4]

A complex metabolic, hormonal, neurological and immunological relationship exists between the microbiome and the host. This molecular cross-talk is critical in regulating many physiological processes. Changes in the composition or function of the gut microbiome can have profound consequences, both negative and positive, on the host. Cohort studies that compare the gut microbiome profiles from healthy and diseased patients have revealed a correlation between many disease states and a person's gut microbiome profile. An altered microbiome that is associated with a disease is often referred to as dysbiosis. Whether dysbiosis is the cause of a disease or the effect of the disease, is poorly understood in most cases and requires further studies (eg, longitudinal and intervention strategies) to determine cause-effect. Another important finding is that no two individuals share the same microbiome, including identical twins. In fact, healthy individuals that are of similar age and demographic have vastly different gut microbiome profiles. This has thwarted our attempts thus far to try and define what a "healthy" microbiome looks like. In general, however, it is thought that higher levels of taxonomic diversity (richness) is an indicator of a "healthy" gut along with the absence of pathogenic species.

Infants become inoculated with their initial microbiome during delivery. Studies have demonstrated that different delivery methods (eg, vaginal vs. caesarian) lead to different microbiome profiles in the infant.[5] It had been thought that, in utero, infants were sterile; however, in 2013 a study found bacteria in nearly 1/3 of placental samples[6] bringing this into question. Diet also plays an important role in the development of the infant gut microbiome. For example, human breast milk contains oligosaccharides that are unrecognizable to the infant but are ably metabolized by certain species of gut bacteria.[7,8] Therefore, human breast milk has evolved to nourish the infant and the infant's gut microbiome. Early development of the infant gut microbiome plays a critical role in the development and function of the immune system, both innate and adaptive. It is estimated that approximately 75% of the body's immune cells reside in the gut,[9] and there is mounting evidence suggesting that autoimmune disorders, like inflammatory bowel diseases, originate in and are modulated by the gut microbiome. Industrialized countries have experienced a dramatic rise in the prevalence of allergic and autoimmune diseases over the last four decades. The "hygiene hypothesis" or "microbial exposure hypothesis" postulate that this rise is attributed to the increasingly sanitary lifestyle of developed countries.[10,11] The connection between the human microbiome and its influence on immune system development and function has been described in great detail in two recent books titled "Missing Microbes" and "Dirt is Good" that were published by leaders within the scientific community.[12,13]

Until recently, the human microbiome remained an underappreciated and understudied target for novel strategies to diagnose and treat disease. The prevalence of diseases that may be rooted in the perturbation of the gut microbiome (eg, irritable bowel syndrome,[14–17] chronic idiopathic constipation,[18,19] colorectal cancer,[20,21] and obesity[17,20,22–26]) are increasing with insufficient alternative explanations.[27,28] Obesity is a complex disease with multi-factorial origin, a portion of which may be due to the composition of the gut microbiome.[20,28–37] Some of the most impressive work on the gut microbiome has come from the field of obesity research, including the fecal transplant from subjects (twins) with or without obesity into mice. These mice were then challenged with a high fat diet; the mice receiving the lean microbiome remained lean while the mice receiving the obese microbiome developed obesity.[38] What is clear from this experiment is that the gut microbiome is a powerful determinant of the phenotype of its host.

The diet is a source of microbiota and a source of fuel for the microbiota in the gut microbiome. Alteration of the diet has been estimated to govern the composition of the gut microbiota almost five-times more than genetics and is a modifiable risk factor.[29,39–41] While short term changes in the diet may produce transient alterations to the gut microbiome, a long term dietary pattern change may lead to significant alteration in composition.[29,42–47] It has been difficult to understand or control the diet in humans well enough to definitively determine the effect of their regular diet, which is why much work has been conducted in animal models, small feeding studies, or supplementation studies.

The diversity of the diet as well as food quality[48] are primary indicators of the composition of the gut microbiome with more diverse and higher quality diets leading to more diverse and purportedly healthier gut microbiota.[36,47] This is particularly true of plant-based foods, which contain various types of dietary fibers; the more diverse the fibers, the more diverse the microbiota.[47,49,50] In seniors, loss of diet diversity and quality after transitioning to residential care has been linked to frailty, inflammation, and poor clinical outcomes.[36,51,52] Further, the diversity and composition of the microbiome varies greatly along the length of the digestive tract, which may be due to differing exposure to dietary constituents. For example, only 15% of carbohydrates (mostly fiber), 5–34% of protein, and very little fat make it from the mouth to the distal colon. This means that gut microbiome samples from the small intestine could vary greatly from that of stool, which is the sample in which most research on the gut microbiome has been conducted and the focus of this review.

In this systematic evaluation of the review literature, we aim to assess the current understanding of the interactions between nutrition and the gut microbiome in healthy adults. A solid understanding of the interactions between nutrition and the gut microbiome in healthy adults will form the foundation for understanding the role of nutrition and the gut microbiome in disease prevention and treatment.

METHODS

In conjunction with librarians at our institution, PubMed and Google Scholar database searched were conducted in March 2018 and August 2018, searching for all medical literature articles relating to nutrition and the gut microbiome. The search strategy was adapted for each database and incorporated both subject terms and free text terms, as applicable. Key PubMed search terms were microbiome, gastrointestinal microbiome, microbiota, microbial, gut, nutrition, nutrient, food, and nutritive value—for example (((((nutrition*) OR nutrient*) OR "Food"[Mesh]) OR "Nutritive Value"[Mesh])) and (((((((microbiota) OR microbial) OR microbiome)) and gut)) OR "Gastrointestinal Microbiome"[Mesh]). Google Scholar search terms included "gut microbiome" nutrition review and "gut microbiome" nutrient review. The PubMed search resulted in 58 articles, with an additional 28 records identified on Google Scholar (Figure 1). Additionally, the Cochrane Library search returned no results. E.C. and L.A.F. independently screened titles and abstracts based on pre-identified inclusion criteria: Review articles, in the English language, published between 2010 and 2018, with healthy human subjects at least 18 years of age. A total of 86 articles were independently screened for duplicates and relevance, based on these pre-identified inclusion criteria (Table 1). There were 6 duplicates and 34 articles were excluded during the screening. An additional 8 articles were excluded during independent full-text eligibility assessment. Discrepancies were resolved by an additional independent review by S.A.J. The qualitative synthesis for this systematic evaluation of the review literature included 38 articles in total.

RESULTS

Calories

Dietary macronutrient composition is a determinant of the makeup of the microbiome, allowing some species to grow, reducing the growth of others, and even preventing colonization of some species.[40] Increasing caloric intake while keeping macronutrient composition similar (holding the ratio of carbohydrates-protein-fat relatively constant while increasing overall intake), increases *Firmicutes* and decreases *Bacteroidetes*[32,44] and reduces overall gut microbiome diversity.[45,54] In turn, dietary restriction (reduced calorie intake) increases diversity;[45,54] however, insufficient calories as in malnutrition decreases diversity.[55] Therefore, calorie intake alone is not necessarily predictive of the composition of the gut microbiome. With long-term increased caloric intake, the composition of the gut microbiome may undergo a long-term shift.[32,40] In lean individuals, this may be a result of increased energy harvest in a dose-dependent fashion.[29,32]

It is generally difficult to isolate the effect of calories from that of macronutrients in clinical research. This is the case in undernourished children, who frequently have a developmentally delayed microbiota that typically persists despite treatment or after treatment is discontinued.[29,56] Thus, inadequate nutrition may serve as a persisting determinant of the composition of the gut microbiome rather than simply insufficient calories. Despite this potentially important relationship, there has been little research on undernutrition and the gut microbiome in part due to the many potential confounders.

Carbohydrates

A polysaccharide (polymeric carbohydrates) rich diet may facilitate more complete energy harvesting from dietary fiber, decrease inflammation, and prevent noncommunicable and infectious intestinal disease.[29,40,57,58] When these polysaccharides come mostly from plants, they are largely fuel for the microbiota—resistant starch,

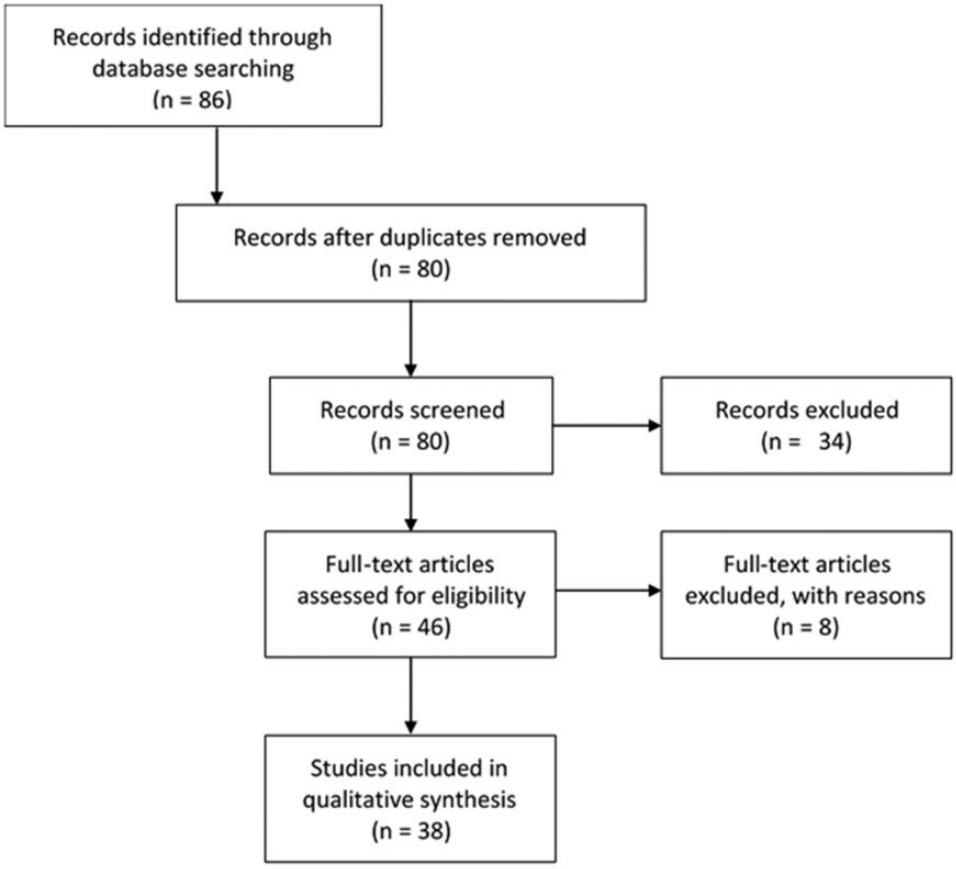

Figure 1 **PRISMA flow diagram for systematic review of nutrition and the gut microbiome.**[186]

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Inclusion criteria
Patients	Healthy adults
Intervention	Diet, supplement, none
Comparator	N/A
Outcomes	Alteration of the gut microbiome or host
Study design	Reviews only

Abbreviations: N/A, not applicable.

oligosaccharides, and non-starch polysaccharides, which may determine the composition of the microbiome.[17,29,40,47,59,60] Resistant starch, oligosaccharides, and non-starch polysaccharides are types of dietary fiber and are not digested in the small intestine like other carbohydrates. Thus, they are available for the microbiota of the large intestine. In keeping with this, a high fiber diet correlates with a microbiome consisting of polysaccharide-utilizing microbiota with lower protein fermentation products and fewer bacteroides and clostridia.[18]

The form and type of carbohydrate may alter the response of the microbiome. For instance, whole oat flakes (0.53–0.63 mm) have been shown to increase *Bacteroides–Prevotella* group bacteria while larger flakes (0.85–1.00 mm) increased bifidobacteria *in vitro* despite the fiber being of the same type (β-glucan).[60,61] *Prevotella* is generally more abundant in those with a plant-based diet.[36,45,51,62] Further, which microbiota reside in the gut may be dependent upon the makeup of the gut mucus glycan in a diet-dependent fashion (mouse model), further complicating this relationship.[36,63] In a reciprocal fashion, microbiota mediated colonic mucus deterioration can occur when the gut microbiota are deprived of dietary fiber or Bifidobacteria.[64,65]

Fiber and short chain fatty acids. There is significant heterogeneity within bacterial species in their ability to ferment (digest) different types of fiber. Short chain fructooligosaccharides (FOS) can be fermented by many of the gut microbiota.[47,66,67] *In vitro*, some, *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Lactobacillus*, and *Roseburia*, can digest oligofructose.[47,66,67] Only very few are able to digest long chain fructans.[47,66,67] Additionally, bacteria may feed off the by-products of other bacteria, a process known as cross-feeding.

When the microbiota ferment fiber, they produce Short Chain Fatty Acids (SCFAs), most copiously

butyrate, acetate, and propionate. Less abundant SCFAs include formate, valerate, and caproate. SCFAs are produced in the large intestine, primarily in the proximal colon with concentrations decreasing in the distal colon.[47,60] These SCFAs account for as much as 10% of our energy requirements with butyrate being absorbed by the cells of the epithelium of the colon.[29,40,41,60,68,69] This process of energy harvesting from otherwise indigestible carbohydrates increases the efficiency of extraction of calories from the diet. Locally, SCFAs like butyrate serve as crucial nourishment; the cells of the epithelium of the colon undergo autophagy, ordered disassembly, without butyrate.[29,40,41,47,55,70–72] The majority of butyrate formation comes from species such as F. *prausnitzii* and *Roseburia*.[41,73] Butyrate may also prevent carcinogenesis[74] and inflammation[75] in these cells.[40,44,47,52] Systemically, acetate enters the citric acid cycle and propionate is a component of gluconeogenesis.[29,40,41,47,55,60,76] While both propionate and acetate are found in circulation, only acetate has been shown to cross the blood-brain barrier.[47] Though, propionate has recently been shown to interact with the blood-brain barrier, potentially protecting it.[77] SCFAs have also been shown to improve absorption of dietary minerals such as calcium,[40,44,55,78,79] aid in water absorption,[44] and alter intestinal permeability,[44,47] which may affect nutrient absorption and the barrier function of the gut. Another product of fermentation is carbon dioxide, over-production of which can lead to symptoms of gas, bloating, and abdominal discomfort; thus, there may be a sweet spot for gut microbiome fermentation, which balances SCFAs and gas production.

Generally, fiber has been shown to increase diversity in the gut microbiota, which is seen to be a marker of a "healthy" gut microbiome.[28,29,47,80–84] The *Prevotella* enterotype is common in those with a high fiber diet with fewer *Bacteroidetes* and *Actinobacteria* and more *Firmicutes* and *Proteobacteri*.[44,62] Increased resistant starch intake has been shown to increase the abundance of *Ruminococcus bromii* (*Clostridia* class)[17,42,85,86] and *Eubacterium rectale*.[86]

High fiber diets have been shown to accelerate intestinal transit time due to the bulk-forming capacity of fiber.[17,40,47,87] Intestinal transit time in turn affects the gut microbiome: Transit time is directly correlated to the prevalence of slow growing species eg, methanogens[40,88] and the total bacterial count.[17,87] As slow growing species decline in prevalence with accelerated intestinal transit time, sulphate reducing bacteria seem to fill this niche.[40,88] Additionally, the production of SCFAs is stimulated, reducing the pH.[17,40,44,87,89] SCFAs then accelerate intestinal transit time by stimulating gut motility,[40,44,71,89] creating a positive feedback loop.

The reduced pH from SCFA production may play a role in reducing the growth of bacteria that may cause disease, eg, *Enterobacteriaceae* like *E. coli* and *Salmonella*. Reduced pH may also reduce commensal bacteria that tend to occur in lower proportions in a healthy microbiome such as *Bacteroides* spp., *Bifidobacterium* spp., *Firmicutes*, and *Proteobacteria* and increase beneficial (butyrate-producing) microbiota such as *Eubacterium rectale* and *Faecalibacterium prausnitzii*.[17,40,60,90–93]

SCFAs have been shown to improve insulin sensitivity and increase energy expenditure in a mouse model of obesity.[40,94] In humans, SCFAs have been linked to hormonal appetite regulation via receptors in the gut and glucagon-like peptide 1 (GLP-1), potentially indicating that the decreased fiber intake in the modern Western diet may have a causal role in the obesity epidemic.[29,36,37,40,41,44,47,55,95] Decreased appetite is associated with a high *Firmicutes* to *Bacteroidetes* ratio, likely by stimulating appetite suppressing hormones, eg, leptin and peptide YY.[29,36,37,44,55] SCFAs have also been shown to alter gene expression by inhibiting histone deacetylase (epigenetic alteration).[37] Further research is needed to determine the exact mechanisms behind these potential benefits of SCFAs.

Seniors tend to have a microbiome less able to produce SCFAs.[40,51,52,79,96,97] This is two-pronged. First, the senior microbiome contains fewer butyrate-producing microbiota such as *Clostridium* cluster XIVa and cluster IV, *Faecalibacterium prausnitzii, Eubacterium rectale*, and *Roseburia* group[40,41,52,96,97] with a reduced ability to produce butyrate, acetate, and propionate.[40,51] Second, senior diets are frequently lower in fiber,[36,79,98] leading to bacterial protein metabolism and the harmful by-products of branched chain fatty acids, ammonia (from increased pH[44]), and phenols.[21,41,79] With a low fiber diet, this reduction in butyrate production coupled with harmful by-products has also been observed in a wider age range (21–74 years, mean 56 years).[43,99] In contrast, cohorts in France and Sweden have been observed to have no significant differences by age.[100,101] This is in keeping with recent work highlighting health status, medications, and lifestyle, which are associated with age, as major drivers of microbiome composition rather than age itself.[102] Therefore, the observed correlations of gut microbiome composition with aging may not be causative, which will require the removal of age-associated confounders to determine.

FODMAPs: Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. FODMAPs are as subset of carbohydrates including fructose, lactose, fructans (inulin), galactans, and polyols (eg, sorbitol and xylitol),

which can be precipitously fermented by the gut microbiota. In susceptible patients, FODMAPs can lead to diarrhea, constipation, gas, bloating, and cramping. A low FODMAP diet has been shown to decrease irritable bowel syndrome (IBS) and functional bloating associated symptoms.[40,103] Low FODMAP diets work to reduce or eliminate high FODMAP foods, including garlic, onions, wheat, and many fruits and vegetables. Breath hydrogen testing, the same test used to diagnose small intestinal bacterial overgrowth (SIBO), may be used to determine fructose and lactose malabsorption and tailor the low FODMAP diet.[40,104] This is particularly notable, as elimination of SIBO, invasion of large intestinal microbiota into the small intestine, has been shown to ameliorate symptoms of IBS.[40,105]

While SCFAs have been associated with various markers of gut health (or lack of disease), high concentrations of SCFAs may be too much of a good thing in IBS. The microbiota in IBS is enriched with bacteria that produce SCFAs. This may lead to high concentrations of SCFAs such as butyrate, which has been associated with noninflammatory colonic hypersensitivity in a rodent model[106] and may overstimulate motility in the small intestine leading to abdominal pain and cramping[107] in humans.[40] The symptoms of IBS are in line with that of high concentrations of SCFAs; perhaps, the low FODMAP diet acts to reduce SCFAs by reducing the substrate.

Prebiotic supplements. Prebiotics are a specific type of fiber that has been shown to increase the growth or metabolism of members of the microbiota. These include mannooligosaccharides (MOS), pectic-oligosaccharides (POS), xylooligosaccharides (XOS), and galactooligosaccharides (GOS). The majority of research has been on inulin and FOS,[29,41,47,72] which have been shown to increase the prevalence of *Bifidobacteria*,[18,47,100,108] *F. prausnitzii*,[66] and lactobacilli;[60,109,110] accelerate intestinal transit time;[41] reduce inflammation;[58,111–113] and increase fecal butyrate concentrations.[100,109] Inulin and FOS naturally occur in many fruits and vegetables, eg, wheat, alliums (onions, garlic, leeks), chicory, artichokes, and bananas.[47,60,72] Research on inulin and FOS has been predominantly in animal models with a few small clinical trials in humans.[72] Reaffirming that different types of carbohydrates produce different reactions in the microbiome, prebiotics may be beneficial in IBS[72,114] with FOS showing potential for strengthening the intestinal barrier function.[60,115] Prebiotics show no benefit or the potential to exacerbate symptoms of gas and bloating in chronic idiopathic constipation while psyllium, non-prebiotic fiber, have been shown to improve transit time and stool consistency.[18] GOS has been shown to increase *Bifidobacteria*, and butyrate, and reduce markers of inflammation in vitro and in vivo.[18,47,109,113,116]

With the wide variety of gut microbiome compositions, there is likely significant variation in the response of individuals to supplementation with prebiotics. In fact, some research subjects have been non-responders to prebiotics.[41,47,66,117,118] In one feeding study, the absence of *Ruminococcus bromii* reduced microbial digestion of a resistant starch supplement to 20–30% versus 100% in those with *Ruminococcus bromii* in their gut microbiomes.[42,47] Furthermore, the response of dominant bacterial species, which may be more omnivorous, seem less affected by the diet than those species in lesser abundance or of a more specialist nature,[41,119] which may also result in a delayed response to dietary changes.[17] Such interindividual variation has led to mixed results between studies of many elements of the diet, leaving us with more questions than answers in many cases, especially outside of the realm of fiber.[29]

Fat, protein. Not surprisingly, a high fat, high protein, low fiber "Western" diet does not seem to be good for humans or the microbiome. Western diet correlates with the *Bacteroides* enterotype with more protein and fat utilizing bacteria, fewer enterococci and *E. coli*, and less microbial diversity.[27,29,44,45,60,120] A high fat diet may increase bile acids and fat in the large intestine.[60] Individuals on a high fat diet tend to exhibit more *Bacteroidetes*, *Actinobacteria*, and *Alistipes*; few *Firmicutes*, *Proteobacteri, and Bifidobacter*; less butyrate and total SCFAs; and decreased intestinal transit time.[36,44,60,62] However, the effect of a high fat diet on an individual appears to be largely determined by the composition of their gut microbiome, at least in rodent models,[39,40,44,121–123] which is likely mediated by high fat diet-induced chronic inflammation, endotoxemia, and plasma lipopolysaccharide (LPS) originating from the gut microbiota via compromised intestinal barrier function.[36,124–128] Confirmation of these findings and further studies in humans are necessary before conclusions can be made about the potential causal link between the diet and the gut microbiome.

Additionally, different types of fat may have differing effects on the gut microbiota, but little research has been done on this topic.[44] Mice fed a high fat diet using palm oil showed significant detrimental effects on the microbiome compared to olive or safflower oil: Increased *Firmicutes* to *Bacteroidetes* ratio, more *Clostridium* (cluster Xi, XVII, XVIII), and reduced diversity.[44,129] Children with a high monounsaturated fatty acid (MUFA), eg, macadamia nut or olive oil, intake tend to have fewer bifidobacterial and more *Bacteroides* spp,[60,130] a healthier composition. Polyunsaturated fatty acids (PUFA), such as Ω-3

(seafood) and Ω-6 (linoleic acid), intake is also associated with a healthier microbiome composition (fewer bifidobacteria).[60,130] Further, conjugated linoleic acids (CLA), Ω-6, appears to ameliorate the detrimental effects of a high fat diet in mice.[44,131] Therefore, MUFAs, PUFAs, and CLA may be key to microbiome composition while other fats may be detrimental.

A high protein diet has been linked to increased *Bacteroides* spp. and clostridia and decrease *B. adolescentis* and *Roseburia/E. rectale* group.[43,60,132] While only 10% of dietary protein reaches the large intestine, some of the microbiota utilize protein as a nitrogen source, including *Streptococcus*, *Bacillus*, *Propionibacterium*, Staphylococcus, *Bacteroide*, and some *Clostridium*.[44] In this process, which predominantly takes place in the distal colon,[60] SCFAs are produced along with branched chain fatty acids, phenol compounds, amines, sulphides, and ammonia—a milieu of beneficial and harmful compounds.[44,55,60] Of note, protein metabolism produces L-carnitine, the substrate of bacterial fermentation to produce trimethylamine N-oxide (TMAO).[44,45,133] TMAO has been linked to atherosclerosis and colorectal cancer.[133–135] In 2011, the World Cancer Research Fund conducted a meta-analysis that concluded that red meat consumption is associated with increased risk of colorectal cancer, while dietary fiber is protective.[60,136] There appears to be a relationship between nutrient imbalance and detriment from a high protein diet.[44,137,138] Specifically, a high fiber, high protein diet may lead to reduced transit time (from the fiber), limiting exposure time to any harmful by-products from protein metabolism, and, thus, reduce the risk of colorectal cancer.[44]

Micronutrients

Digestion and absorption of nutrients in humans occurs predominantly in the small intestine and stomach: 85% of carbohydrates, 66–95% of protein, and all fats.[29,139,140] Therefore, the colon and the bulk of the gut microbiome is exposed to food after much of the nutrition (that the host can digest) has been removed. In this symbiotic relationship, the microbiota feed off the remaining nutrients, including fiber that is not digestible by the host. The microbiome in turn plays a role in absorption and production of energy and micronutrients including essential vitamins, which are required for vital bodily functions and cannot be produced by the host. Body stores and pools of some micronutrients are significantly higher than the composition of the diet would suggest due to absorption of these micronutrients in the colon, which are produced by the microbiota. This is the case for vitamin K[141,142] and many of the water soluble B vitamins: Thiamine (vitamin B1),[143] riboflavin (vitamin B2),[144] niacin (vitamin B3),[145] pyridoxine (vitamin B6),[145,146] biotin (vitamin B7),[147] and folate (vitamin B9).[28,36,55,72,145,148,149]

B vitamins.

Thiamine (Vitamin B1)

Thiamine is utilized in digestion and carbohydrate metabolism as well as in the electrolyte flow in nerve and muscle cells. Risk factors for deficiency include alcoholism, vomiting, SIBO, acid reducers such as proton pump inhibitors (PPIs), and malabsorption, which may be caused by ingesting caffeine and/or tannins with food.

The gut microbiota synthesize thiamine in significant amounts and may contribute to the nutritional status of the host.[150]

Riboflavin (Vitamin B2)

Riboflavin is important for energy production and metabolism including in the metabolism of other B vitamins and iron as well as antioxidant activity. Risk factors for deficiency include alcoholism, malnutrition such as anorexia, lactose intolerance, hypothyroidism, and high levels of physical activity.

The riboflavin found in dairy is due to fermentation by microbes and the human gut microbiota can produce riboflavin, the significance of which has yet to be determined.[150]

Vitamin B6 (Pyridoxine)

Vitamin B6 is an essential cofactor in protein metabolism with key effects on the function of the nervous system, hemoglobin, tryptophan, steroid hormones, and nucleic acids. Deficiency in vitamin B6 is seen mostly in alcoholism.

While the microbiota depend on vitamin B6 for some enzymatic activities, especially *Eubacterium rectale* and *Porphyromonas gingivalis*, the relationship between dietary vitamin B6 and the gut microbiota is largely unexplored.[150,151] There may be a positive association between virulence and motility in the pathogen responsible for stomach ulcers, *Helicobacter pylori*, and their ability to produce vitamin B6; however, the importance of this association has yet to be determined.[150,152]

Folate (Vitamin B9)

Folate is required for DNA synthesis and repair, cell division and growth, and red blood cell formation. Risk factors for folate deficiency include alcoholism; use of anticonvulsants, oral contraceptives, and some cancer treatments; SIBO; and malabsorptive disease or surgery, eg, short-bowel syndrome or bariatric surgery.

Folate production is possible for many of the gut microbiota and may be produced in sufficient amounts to significantly affect the intake of this vitamin.[40,150,153] The production of folate occurs with the processing of resistant starch, especially by *Bifidobacterium bifidum* and *longum* subsp. *Infantis*.[40,150,154,155] In rats, microbiota-produced folate has been shown to be absorbed and utilized, but this may not translate to humans.[150] In humans, microbial folate production positively correlates with fecal concentrations of folate, meaning the folate produced by the microbiota may not significantly contribute to folate status due to poor absorption.[150,156]

Vitamin B12 (Cobalamin)

Vitamin B12 is required for DNA synthesis, neurologic function, and red blood cell maturation. Deficiency risk factors include SIBO; digestive diseases or surgeries limiting the small intestine such as Crohn's and Celiac disease; use of metformin, angiotensin-converting enzyme (ACE) inhibitors, acid reducers, colchicine (gout); and following a strict vegetarian or vegan diet, as plants do not produce vitamin B12.

Vitamin B12 is required for microbial metabolism including fatty acids, cholesterol, propionic acid, and branched-chain amino acids; it has been shown to be an essential cofactor in the majority of gut microbiota.[150,157] Along with folate, vitamin B12 regulates microbial gene expression via methylation (epigenetics), which may be involved in the interactions between the genomes of the gut microbiota and the host.[150,158] A minority of the gut microbiota synthesize vitamin B12; eg, *Propionibacterium freudenreichii*, *Listeria innocua*, and *Lactobacillus reuteri*; indicating that most gut microbiota compete with the host for dietary vitamin B12 to some extent.[150,158] It is not known if this is a significant contributor to vitamin B12 deficiency in humans. Furthermore, microbiota-produced vitamin B12 may not be bioavailable to humans due to lack of receptor-binding for its absorption in the large intestine, the site of microbial production.[55,150,158]

Vitamin K. Unlike most of the B vitamins produced by the gut microbiota, vitamin K is a group of fat soluble micronutrients. Vitamins K are important for production of prothrombin, a blood clotting factor, and thus prevention of exsanguination. Vitamin K1 (phylloquinone), the most familiar of the K vitamins, is found in plants such as green leafy vegetables. Vitamin K2 (menaquinone), the storage form of vitamin K, is a group of compounds found in meats, cheeses, eggs, and from bacterial production[142,159–161] such as fermented foods or the gut microbiota. Vitamin K2 forms vary in size due to their number of isoprenoid units.[150] Vitamin K2 status is negatively associated with heart disease and osteoporosis; however, the contribution of microbiota-produced vitamin K2 to host status or these health outcomes has not been established.[150,162] It is known that the gut microbiota uses vitamin K2 as electron carriers, a critical function.

In humans, vitamin K deficiency is not thought to be common. Deficiency is typically seen in newborns, who are given an injection of vitamin K after birth, and in malabsorptive disease/surgery, eg, cystic fibrosis, Celiac disease, or ulcerative colitis. Additional risk factors for deficiency include use of anticonvulsants and cholesterol-lowering medications, which limit the fat absorption necessary to absorb vitamin K in the small intestine. Some absorption of vitamins K may occur on the large intestine as well.

Vitamin A. Vitamin A is a group of fat-soluble compounds that include retinol, retinal, retinoic acid, and provitamin carotenoids (eg, β-carotene). Vitamin A is a key contributor to eye health and vision, especially night vision, as well as cell growth and wound healing. While vitamin A deficiency is uncommon in the United States, it leads to a significant burden of disease in developing countries. Risk factors include pancreatic insufficiency and malabsorptive surgery.

Emerging research has shown microbial production of β-carotene; however, the important next step of cleavage to form retinal has not been demonstrated.[150,163] There is some indication that the anti-inflammatory effect of *B. infantis* requires vitamin A in the form of retinoic acid, which may be sourced from the cells of the large intestine.[150] In fact, vitamin A has been shown to play a preventative role in cancer of the large intestine along with vitamin D.[150,164]

Vitamin D. Vitamin D is a fat-soluble vitamin as well as a steroid hormone, giving it wide-ranging effects. Traditionally, bone health has been the key area for vitamin D. In the last two decades, extraskeletal effects, eg, immune function and regulation of gene expression through the vitamin D receptor (VDR), have been elucidated. Risk factors for vitamin D deficiency predominantly focus on insufficient sun exposure (latitude, season, indoors, sunscreen/melanin, etc.), as the diet is a poor source of vitamin D. In the gut, as in many cells throughout the body, vitamin D, bound to the VDR, heterodimerizes with the vitamin A-retinoid X receptor (RXR) complex. Thus, vitamin D insufficiency may lead to altered gut barrier function, potentially contributing to the development of intestinal disease or cancer.[150,165]

The VDR does not occur in prokaryotic cells; therefore, the microbiota are likely not directly influenced by vitamin D. Indirect effects may include

alteration of host immune function resulting in an inflammatory state and/or reduced tolerance to commensal bacteria.[150] Additionally, SCFAs from the gut microbiota enhance the ability of vitamin D to stimulate formation of the antimicrobial peptide cathelicidin, which is important for the immune and barrier functions of the gut, by increasing gene expression through the VDR-RXR complex.[150]

Iron. Iron is the backbone of oxygen transport as the central component of hemoglobin and myoglobin. Iron is also crucial for many cellular functions including energy production and DNA synthesis. Iron status is tightly regulated as iron is excreted in only small amounts except in menstruating women and those with significant blood loss. The other important risk factor for deficiency is insufficient gastric acid from acid reducers or bariatric surgery, which limits iron absorption.

In individuals with iron-deficiency anemia, the gut microbiome lacks *Lactobacilli*.[28,55,166] The directionality of this relationship has not been established; however, *Lactobacilli* require a substantial amount of iron for growth, a potential limitation for growth in those with iron-deficiency anemia.[55] Additionally, production of SCFAs reduce the pH in the large intestine, promoting iron absorption.[55]

Zinc. Zinc is crucial for many wide-reaching functions in part due to its role in gene expression and replication through zinc fingers and its interactions with the nutrients copper, iron, calcium, folate, and vitamin A. Mild zinc deficiency may occur due to malnutrition, severe or persistent diarrhea, malabsorptive or inflammatory bowel disease (Celiac and Crohn's disease, ulcerative colitis, short bowel syndrome/bariatric surgery), alcoholism, chronic renal disease, sickle cell anemia, seniors, strict vegetarians and vegans, and those using medications such as antibiotics, metal-chelating agents, anticonvulsants, and diuretics. Severe zinc deficiency is rare.

Supplementation with ZnO may increase Firmicutes such as *Lactobacillus*, but research is limited and mostly in animal models.[28,167]

Non-nutritive bioactive food components

Polyphenols. Polyphenols are a class of chemicals produced by plants including those consumed in the typical diet, eg, flavonoids, phenolic acids, stilbenes, and lignans. Polyphenols have been linked to beneficial effects on health such as preventing cancer and heart disease.[28,168–170] Approximately 90% of ingested polyphenols arrive in the large intestine due to limited absorption, allowing for concentrated interaction with the gut microbiome.[28,170] The gut microbiome then may process the polyphenols in a way that makes them more bioavailable to the host and thus magnifying any potential effect and/or the polyphenols may serve an antimicrobial function against pathogenic bacteria.[28,169,170]

Polyphenols may mitigate the detrimental effects of a high fat diet on the gut microbiome by increasing *Akkermansia muciniphila* and decreasing the *Firmicutes* to *Bacteroidetes* ratio according to a mouse model.[44,171] It is possible that the effect of polyphenols on the gut microbiome is greater than that of the macronutrient composition of the diet, but further research is needed to establish this.[45,172]

Flavonols such as quercetin and catechin, isoflavones such as puerarin, anthocyanins, ellagitannins, resveratrol, and pterostilbene are likely to have effects on the gut microbiome as well, but there is insufficient research to-date to determine this relationship.

A body of literature exists on this topic outside the scope of this systematic evaluation of the review literature in healthy adults, which warrants further exploration.[173–179]

Wine

The polyphenols found in wine include flavonols, anthocyanins (predominant in red wine), hydroxybenzoic and hydroxycinnamic acids (predominant in white wines), stilbenes, and phenolic alcohols, making wine a good source of polyphenols in general.[180] Of these, procyanidins, conjugated polyphenols, esters, and phase II metabolites may be found in the colon,[181] where they may be transformed by the gut microbiota into highly active metabolites.[180] Daily red wine intake has been linked to many health benefits including gut and heart health, which may be related to the metabolism of polyphenols by the gut microbiota.[180,181] The correlation between wine polyphenols and health benefits, as well as the potential need for doses much larger than typically consumed, has led to the introduction of numerous supplements and functional foods for consumer use. However, the research base in this area is still emerging.

Wine and the crushed grapes from the wine making process have been shown to have antimicrobial activity against pathogens such as *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella spp.* in vitro.[180] Queipo-Ortuno et al worked to isolate the effect of red wine polyphenols with and without alcohol on the gut microbiome. [181] Gin led to an increase in *Bacteroides* and *Clostridium* and loss of *Prevotellaceae*.[60,181] Red wine polyphenols (with or without alcohol) resulted in more *Bacteroidetes*, while dealcoholized wine showed increased *Fusobacteria*.[181] A significant increase in the *Proteobacteria*, *Firmicutes*, and *Bacteroidetes* phyla were observed following red wine, but not with gin or de-

Table 2 **Isolated wine polyphenols may alter the composition of the gut microbiome**

	Inhibit pathogenic bacteria	Potential probiotic effects
Wine polyphenols		
Flavan-3-ols	*Clostridium difficile*	Promote *Clostridium cocccoides–Eubacterium rectale* group, *Bifidobacterium* spp.; inhibit *Clostridium histolyticum* group
(+)-Catechin		
(−)-Epicatechin		
Gallic acid	*Clostridium perfringens*	
3-*O*-methyl gallic acid		
Microbial-derived phenolic acids		
Caffeic acid	*Staphylococcus* spp., *Escherichia coli, Salmonella* spp.	Little effect on *Lactobacillus* spp. and *Bifidobacterium* spp.
3-(4-Hydroxyphenyl)-propionic acid		
3-Phenylpropionic acid		
4-Hydroxyphenylacetic acid		
Dihydroxylated phenolic acids	*Salmonella* spp.	

Sources: Requena et al. (2010), Lee et al. (2006), Alakomi et al. (2007), and Tzounis et al. (2008).

alcoholized red wine, indicating a synergistic interaction between red wine polyphenols and alcohol.[181]

The individual polyphenols of wine have been isolated and studied individually; however, it is likely that there is an effect of the food matrix on their actions, including synergistic interactions among the polyphenols.[180] The potential effects of only a handful of the many polyphenols in wine are highlighted in Table 2, illustrating the complexity of studying foods with many bioactive components.[180,182–184]

Berries

Berries may have beneficial effects on the gut microbiome. Berries high in ellagitannins (100 g each of strawberry purée, frozen raspberries, and frozen cloudberries daily) have been reported to alter the prevalence of *Ruminococcaceae* and *Lachnospiraceae*, which are most of the butyrate producing microbiota.[60,185] Isolated berry-polyphenols have been shown to weaken *Salmonella* by increasing the permeability of their outer membrance.[60,183]

Tea

Teas contain polyphenols such as epicatechin, catechin, gallic acid, and caffeic acid.[60] An extract of tea retarded growth of potentially harmful bacteria including *Clostridium perfringens, Clostridium difficile*, and *Bacteroides* spp. while largely sparing commensal bacteria such as *Clostridium* spp., *Bifidobacterium* spp., and *Lactobacillus* sp.[60,182]

Cocoa

A randomized controlled trial of cocoa-derived flavanols in healthy humans has shown increased *Bifidobacteria* and *Lactobacilli* and decreased *Clostridia*.[60,186]

Other minor components of food: Food additives

Food additives, contaminants, and other minor food components have the potential to affect the gut microbiome and modify its composition; however, they have largely been excluded in the reviews of nutrition and the gut microbiome. While further research needs to be completed in these areas before specific relationships can be elucidated, work on the effects of non-caloric sweeteners and emulsifiers show promise.[28,187]

DISCUSSION

With advances in DNA sequencing technologies came the ability to measure and describe the human microbiome, leading to a surge in information about the gut microbiome and its role in health and disease in the last decade. As the diet is both a source of microbiota in the gut microbiome and a fuel source for these microbiota, some research in this burgeoning field has centered on the role of nutrition and diet in the composition and function of the gut microbiome. While transient changes in diet are unlikely to lead to significant, durable changes in the microbiome, the typical diet or a long-term dietary change can have robust effects.

The number of calories consumed in the diet does not appear to have a simple linear relationship with the composition or function of the gut microbiome. Rather, too much or too few calories may be linked to dysbiosis, in more of a U- or J- shaped relationship. The macronutrient (carbohydrate, fat, protein) content of the diet is difficult to separate from calories without controlled feeding studies, which limit sample size and generalizability. It is likely that the role of micronutrient intake has confounded that of macronutrient intake in many gut microbiome studies.

Much of the research on the diet has focused on carbohydrates, as plant-based polysaccharides in the

diet serve as fuel for the gut microbiota. In fact, many polysaccharides are fiber (resistant starch, oligosaccharides) and are not digestible by humans alone. Instead, the microbiota metabolizes the fiber, leading to increased energy harvest and other potentially beneficial by-products for the host. The type, amount, and size of these carbohydrates may determine the composition of the gut microbiome with the fiber content of the diet positively correlating with polysaccharide-utilizing microbiota and diversity of the gut microbiome, generally considered to be a marker of health.

The beneficial effects of fiber via the microbiome have been centered on SCFAs, which are required by colonocytes and for intestinal barrier function, improve absorption of dietary minerals like calcium, assist in water absorption, and accelerate intestinal transit. Fiber is a bulk-forming component of stool, which leads to reduced intestinal transit time (independent of the microbiome). Combining this with the ability of fiber to increase SCFA production, leads to a positive feedback loop supporting a speedy intestinal transit time, which is commonly thought to support gastrointestinal and systemic health. SCFAs also may have systemic effects, as they pass into the circulatory system and may cross the blood-brain barrier (at least acetate does). Systemically, SCFAs may have a role in insulin sensitivity, energy expenditure, appetite regulation, and gene expression (histone deacetylase inhibition). The systemic effects of SCFAs are promising; however, most of this work has been done in animal models, which have yet to be translated to humans, or is correlation from observational studies. As with most aspects of nutrition, too much of a good thing (SCFAs) can lead to negative health consequences. This is evidenced by a significant reduction in symptoms in IBS patients on a low FODMAP diet, which may reduce production of SCFAs.

Prebiotic supplements can simplify the study of fiber in humans, as specific doses can be reliably administered. The majority of research in prebiotics has been focused on inulin and FOS and in animal models with several small clinical trials in humans. The role of prebiotics in health and disease is still emerging and looks to be complex with some ailments (IBS) potentially benefiting from prebiotic supplementation and others (idiopathic constipation) showing no benefit or exacerbation of symptoms. The wide range of response to prebiotic supplementation is indicative of the vast interindividual differences in the composition and function of the gut microbiome.

Protein metabolism by the microbiota may lead to potentially dangerous by-products such as TMAO. These relationships may be dictated by the composition and function of the gut microbiome and gut health. For instance, an omnivore on a high fat, high protein, low fiber diet may have significant production of TMAO in their colon coupled with a slow intestinal transit time, resulting in colorectal cancer. In contrast, an omnivore on a high fat, high protein, high fiber diet may have production of TMAO (at similar or lower levels) coupled with a quick intestinal transit time and avoid colorectal cancer due in large part to the decreased contact time from the faster intestinal transit time.

The bidirectional relationship between micronutrition and the gut microbiome is beginning to emerge. The microbiota both utilize and produce micronutrients with intake of some micronutrients being sufficiently lower than nutritional status would suggest due to the contribution of the microbiome, primarily the B and K vitamins. The study of non-nutritive food components and the gut microbiome is in its infancy; however, research to date is promising, especially as it relates to polyphenols. The role of other components of food such as food additives and contaminants warrant exploration and are a significant research gap to-date.

Emerging evidence suggests that bacterial biofilms form around food particles in the gut and that these represent unique microbial communities.[45,172] These food-associated bacteria are distinct from the free microbiota, producing different signals.[45,172] The role of such food-associated bacteria is a promising new area of research on the gut microbiome and nutrition.

As mentioned in the introduction, there is no consensus within the scientific community on what defines a healthy gut microbiome. The reason for this might have become apparent from this review; in some cases, a particular phylum is associated with a positive outcome while in other cases the same phylum is associated with a poor outcome. The ratio of different phyla (relative abundance) has also been implied to be a marker of "good" vs. "bad," but these trends are usually debunked by additional studies looking at different cohorts. Biomarkers of gut health are elusive due to measurement challenges. As the cost of DNA sequencing technologies continue to plummet, researchers will increasingly adopt more granular measurements that identify microbial content at the species, or even strain, level. These (whole genome shotgun) measurements also identify the genes present within the microbial consortia. Gene-level reports allow for the prediction of metabolic and biochemical potential of a microbial consortium.

Metabolomics is a burgeoning 'omic technology that has the potential to transform our understanding of microbiome function.[188] DNA-based measurements identify the taxonomic assets of a microbiome and, to a much lesser extent, the metabolic potential of a microbiome. Metabolomic measurements are able to identify

1000's of small-molecule metabolites from a microbiome, including SCFAs, TMAO, and other metabolic byproducts of the gut microbiome. Metabolic profiles can be compared across cohorts to identify functional/metabolic differences. Previous metabolomic studies of the human gut microbiome have suggested that taxonomically diverse microbiomes have similar metabolic activities. That is, metabolic function is conserved, not taxonomy, and similar metabolic profiles can be achieved by vastly different taxonomic profiles. Thus, homeostasis is achieved at the metabolic level, not the taxonomic level. Metabolomic profiling might be the critical element that is needed to identify biomarkers that are diagnostic indicators of gut health.

CONCLUSION

Diet and nutrition, notably fiber, affect the composition of the gut microbiome. This, in turn, affects a wide array of metabolic, hormonal, and neurological processes that influence our health and disease. Currently there is no consensus in the scientific community on what defines a "healthy" gut microbiome. Future research must consider individual responses to diet and how the gut microbiome responds to dietary interventions as well as emphasize function (metabolomics) over composition (genomics).

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Supporting information

The following Supporting Information is available through the online version of this article at the publisher's website.

PRISMA 2009 checklist

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