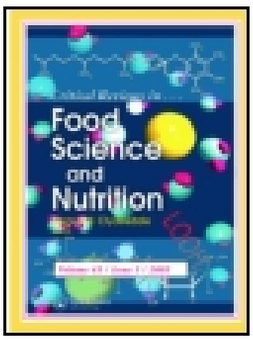

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Jie Cai, Zhongxu Chen, Wei Wu, Qinlu Lin & Ying Liang (2021): High animal protein diet and gut microbiota in human health, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1898336

To link to this article: https://doi.org/10.1080/10408398.2021.1898336

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1898336

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REVIEW

High animal protein diet and gut microbiota in human health

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ABSTRACT

The role of the intestinal flora in health and disease has become a research hotspot. Compared with carbohydrates and fats, proteins are metabolized primarily by microbial fermentation in the intestine. The production of protein fermentation products and metabolites depends on the composition, diversity, and metabolism of the gut microbiota. Several protein fermentation products, including indoles, phenols, polyamines, hydrogen sulfide (H_2S), amines, and carnitine, are toxic. This study analyzes the relationship between high-protein diets (HPDs), the intestinal microbiota, and human health and disease. Long-term HPDs increase the risk of intestinal diseases, type 2 diabetes (T2DM), obesity, central nervous system (CNS) diseases, and cardiovascular diseases (CVD) by producing toxic metabolites in the colon, including amines, H_2S, and ammonia. Short-term HPDs have little effect on the metabolism of healthy individuals under 65 years old. However, meeting the protein requirements of individuals over 65 years old using HPDs is more challenging. The adverse effects of HPDs on athletes are minimal. Natural compounds (plant extracts, whose main constituents are polysaccharides and polyphenols), prebiotics, probiotics, and regular physical exercise improve gut dysbiosis and reduce disease risk.

KEYWORDS

Diet; animal protein; gut microbiota; disease

Introduction

The gut microbiota is a dynamic and complex ecosystem composed of trillions of microbes and thousands of bacterial species (Qin et al. 2010). Microbial activity affects host metabolism, immunity, and nervous system development. The gut microbiota is implicated in health and disease, including neurodegenerative and metabolic diseases. Microbial composition affects dietary energy intake (Turnbaugh et al. 2006). In turn, diet shapes the microbial community structure and activity (David et al. 2014). The effects of dietary changes on the gut microbiota and host health depend on individual differences in the microbial community structure. The microbiome maintains physiological homeostasis by establishing a symbiotic relationship with the host (Requena, Martínez-Cuesta, and Peláez 2018).

The development of the global economy and improvements in living standards have enabled an increase in the intake of protein-rich foods, including meat, eggs, and milk. Proteins provide essential amino acids (AAs). The demand for protein-rich foods is expected to reach USD 90 billion by 2021 (Wilson 2019; Research 2019–2025 (GVR 2019)). The nonprofit Institute of Medicine (IOM) from the American Academy of Sciences recommends a daily protein intake of 0.6 g/kg for adults (Rand, Pellett, and Young 2003), whereas the World Health Organization and the United Nations Food and Agriculture Organization recommend a daily protein intake of 0.83 g/kg for adults (Organization WHO 2007). Moreover, the IOM recommends a protein: energy ratio of 10–30% from the daily dietary protein to total energy intake. A ratio of 15% is equivalent to a protein intake of 0.83 g/kg (Organization WHO 2007; Rand, Pellett, and Young 2003).

It is currently believed that high-protein diets (HPDs) improve human health. For this reason, HPDs are used to achieve weight loss and improve muscle function and quality (Mötteli et al. 2016; Samal and Samal 2018). Nonetheless, proteins are fermented in the colon and can potentially produce gases and toxic metabolites (David et al. 2014). Studies using in vitro and animal models have shown that protein fermentation products favor the occurrence and development of colon cancer and inflammatory bowel disease, especially in extreme diets (Hussain et al. 2019; Windey, De Preter, and Verbeke 2012; Yang and Yu 2018). L-carnitine present in animal protein, especially red meat and processed meat, is metabolized in the colon and produces trimethylamine (TMA), which increases the risk of cardiovascular disease (CVD) (Koeth et al. 2013). Some fermentation products induce dysbiosis, which affects the central nervous system (CNS) and metabolism through the gut-brain-axis and blood circulation, respectively (Sharon et al. 2019; Meijnikman et al. 2018). In addition, the concentration of fermentation products in feces is positively correlated with dietary protein intake (Toden et al. 2007). Therefore, regardless of the intervention duration, protein dietary interventions affect gut microbiota composition and metabolism

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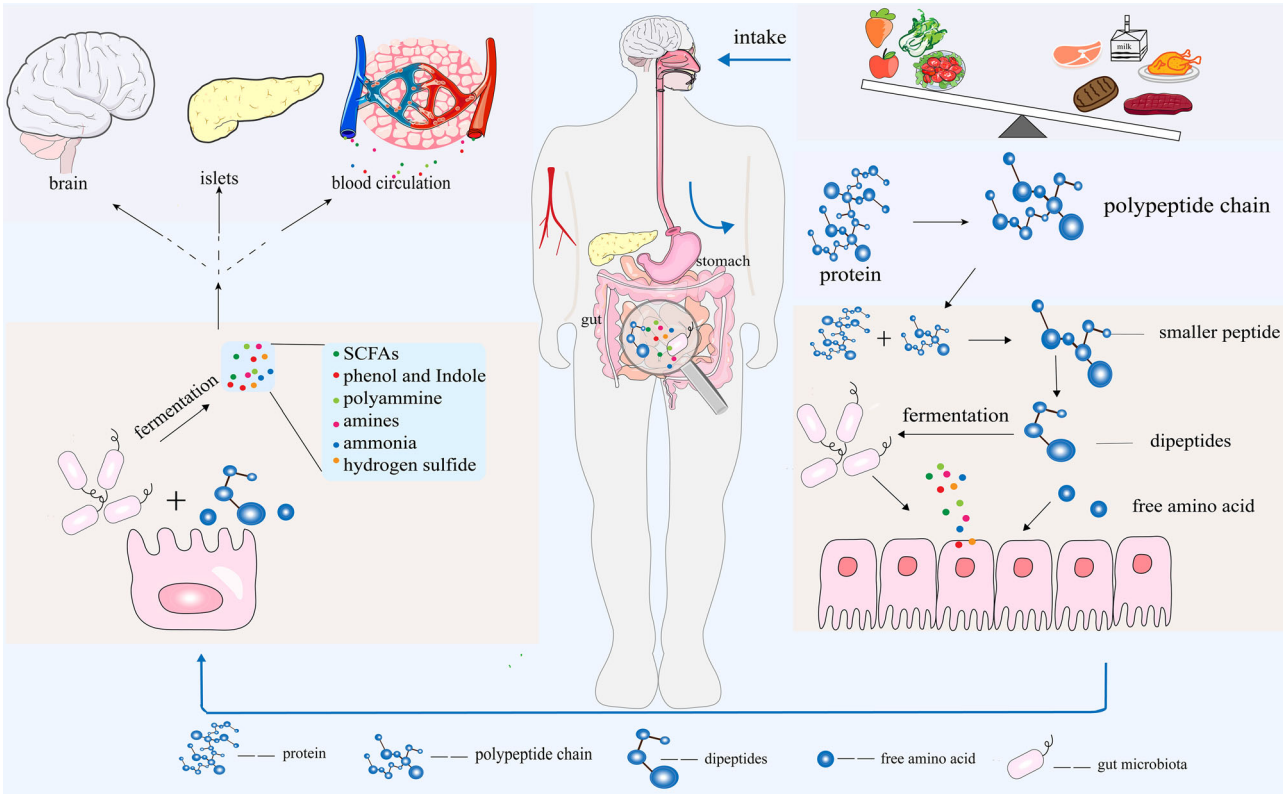

Figure 1. Protein metabolism. Proteins are broken down into peptides and amino acids by digestive enzymes in the stomach, including endopeptidases (trypsin, chymotrypsin, and elastase) and exopeptidases, which catalyze the hydrolysis of internal and terminal amino acids, respectively. Small peptides and amino acids are absorbed by intestinal mucosal cells, enter the hepatic portal vein, and are transported to various tissues and organs. Other food components enter the colon and are fermented by microorganisms into metabolites, which are released into the circulation. This figure cannot be reproduced without author permission.

(Portune et al. 2017). This review investigates the impact of HPDs on the health of populations at risk of diseases, athletes, and the elderly as well as the interactions between protein metabolites and intestinal flora. The studies included in the review were found by searching for the following terms in Medline: "protein diet', "health and disease," "animal protein," "intestinal flora," "elderly," "athlete," "probiotics," and "prebiotics."

HPDs and disease risk

Indole, phenols, polyamines, gases, amines, and TMA affect the intestinal flora as well as host metabolism, immunity, and the nervous system (Portune et al.2016; Windey, De Preter, and Verbeke 2012; Fuller 2012) (Figure 1). Moreover, some of these compounds are implicated in the development and severity of metabolic diseases, such as obesity and diabetes, and neurodegenerative diseases, including Alzheimer's disease (AD) (Diether and Willing 2019).

Intestinal diseases

Dietary peptides and amino acids are mainly transported through the intestinal wall (Hemmings and Williams 1978; Matthews and Laster 1965). A study involving the in-silico analysis of bacterial genomes revealed that pathways for the production of amines and H_2S are used by *Bacillus*, *Clostridium*, *Enterobacter*, *Escherichia*, *Fusarium*, and *Salmonella*. Most of these bacterial genera colonize the human intestine (Kaur, Das, and Mande 2017). Proteins and peptides are digested and absorbed in the small intestine, and undigested products are fermented in the large intestine. All dietary metabolites affect intestinal homeostasis (Zmora, Suez, and Elinav 2019). Although some dietary changes are not enough to cause colorectal cancer (CRC) (Tayyem et al. 2017), HPDs can potentially cause intestinal inflammation and increase the risk of CRC. Indoles and amines react with nitric oxide to form nitrite compounds, which may cause gastro intestinal (GI) cancer in humans (Zhu, Wang, et al. 2014). Colonic bacteria play an indispensable role in maintaining intestinal homeostasis and epithelial integrity. The disruption of microbial community structure may lead to intestinal inflammation, epithelial barrier dysfunction, and bacterial translocation (Clements and Carding 2018).

Metabolic disease

Obesity

Dietary protein metabolism is believed to require more energy than carbohydrate and fat hydrolysis, and the latter two are more likely to cause obesity (Stock 1999). An athlete's weight can be effectively maintained and reduced through exposure to high-protein/low-carbohydrate diets (Cuenca-Sánchez, Navas-Carrillo, and Orenes-Piñero 2015). Rodent studies have demonstrated that obesity can be prevented by increasing the protein to carbohydrate ratio (Madsen et al. 2008). Other studies have also shown that HPDs increase weight loss compared to low-protein diets

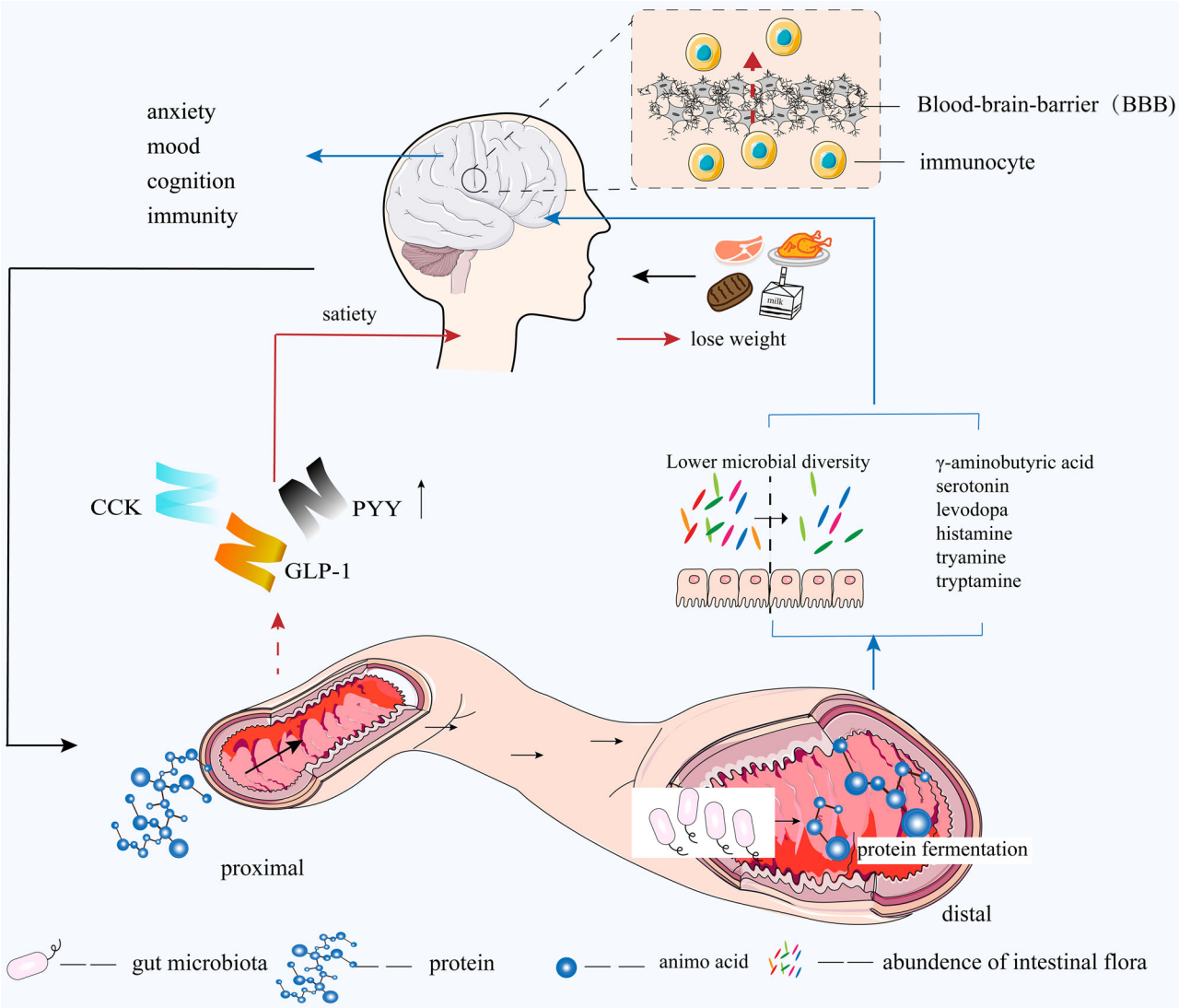

Figure 2. Regulation of appetite and satiety by a protein-rich diet. Proteins stimulate the secretion of hormones CCK, PYY, and GLP-1 in the gastrointestinal tract, which provides signals to satiety centers in the brain via vagal pathways. High-protein diets can potentially reduce intestinal microbial diversity and promote neuroinflammation and CNS diseases by allowing inflammatory cells to cross the blood-brain barrier (red arrows). CCK, cholecystokinin; PYY, peptide YY; GLP-1, glucagon-like peptide 1. This figure cannot be reproduced without author permission.

(Santesso et al. 2012; Campos-Nonato, Hernandez, and Barquera 2017), possibly because satiety hormones, including cholecystokinin (CCK), peptide YY (PYY), and glucagon-like peptide 1 (GLP-1), are secreted in the GI tract and stimulate satiety centers in the brain via vagal pathways (Cuenca-Sánchez, Navas-Carrillo, and Orenes-Piñero 2015) (Figure 2). A rodent study showed that whey-based HPDs can maintain normal muscle and liver histomorphology (Avila et al. 2018), which may be because branched-chain AAs (BCAAs) in whey protein hydrolysates favor the growth of *Bifidobacterium* and *Akkermansia* in the intestine (Yang et al. 2016).

With respect to the negative effects of long-term HPDs, a study in which stool samples were analyzed from four pairs of twin mice discordant for obesity and treated by oral gavage revealed that compared with their thin counterparts, the expression of genes associated with AA degradation pathways was lower in the intestine of obese mice (Ridaura et al. 2013). Research based on rodents suggests that the maintenance of HPDs for weight loss may have a negative impact. The intestinal flora is strongly related to obesity. However, the effect of HPDs on the metabolism of obese individuals is incompletely understood. HPDs can potentially impair intestinal homeostasis Furthermore, epidemiological studies have shown that although dairy products and plant-derived proteins can prevent obesity, animal meat, especially red meat, can potentially cause obesity (Smith et al. 2015; Mozaffarian 2016).

Type 2 diabetes

An increase in insulin resistance and a decrease in insulin secretion may lead to type 2 diabetes mellitus (T2DM) (Grandl and Wolfrum 2018). In particular, hydrogen sulfide (H_2S), a by-product of microbial fermentation, can impair islet function in rats (Wu et al. 2009). H_2S stimulated gluconeogenesis and glycogenolysis and reduced glucose utilization and glycogen storage in mice hepatocytes (Zhang et al.

2013). A study suggested that plasma H_2S concentrations are lower in T2DM patients than in healthy individuals (Jain et al. 2010). Excessive protein intake may increase H_2S concentrations in individuals with T2DM, resulting in decreased glucose utilization. The administration of p-cresol sulfate (derived from p-cresol of protein fermentation) for 4 weeks resulted in peripheral insulin resistance in mice (Koppe et al. 2013). Furthermore, gut microbial activity increased the serum levels of BCAAs, hydrocinnamic acid, and indole-3-lactic acid in T2DM (Pedersen et al. 2016), potentially increasing the concentration of AAs. In addition, phylum *Firmicutes* and class *Clostridia* were significantly reduced in T2DM individuals (Larsen et al. 2010). The butyrate producers *R. intestinalis* and *F. prausnitzii* were significantly lower in women with T2DM, indicating that gut microbes are implicated in T2DM (Karlsson et al. 2012). The diversity of the intestinal flora in T2DM individuals is lower than that in healthy individuals. There is increasing evidence that the intestinal flora is related to the occurrence and development of T2DM, but there is a lack of research on the species responsible.

Central nervous system diseases

There is an intricate interplay between vagal afferent neurons, gut endocrine cells, and bacterial metabolites (Raybould 2010). Enteroendocrine cells express receptors for serotonin, neuropeptides (CCK, GLP, and PYY), and neurotransmitters (dopamine and acetylcholine) (Bonaz, Bazin, and Pellissier 2018). In addition, several AA-derived compounds, including γ-aminobutyric acid, serotonin, levodopa, histamine, tryamine, and tryptamine, impact mood, cognition, and host immunity (Portune, et al. 2017). Autoimmune diseases of the CNS, such as multiple sclerosis (MS), are characterized by the invasion of the CNS by immune cells, including T and B cells and activated monocytes (Adamczyk-Sowa et al. 2017). The percentages of *Bacteroides*, *Faecalibacterium,* and short-chain fatty acid (SCFA)-producing bacteria are lower, while the percentages of *Akkermansia*, Enterobacteriaceae, and *Methanobacter* are higher in individuals with MS (Miyake et al. 2015). The immune system is part of a communication network between intestinal microbes and CNS diseases (Grenham et al. 2011).

A few studies have suggested that the consumption of large amounts of milk, meat, or animal fat increases the risk of MS (Agranoff and Goldberg 1974). In children with autism spectrum disorder (ASD), undigested proteins increase the production of toxic microbial metabolites, which impair epithelial barrier integrity and aggravate disease symptoms (Sanctuary et al. 2018). Animal studies have shown that gut microbial composition and abundance affect the brain (Cryan et al. 2019). Furthermore, some bacterial strains affect animal behavior, and the gut microbiota community structure and function affect the brain microenvironment (Cryan et al. 2019; Quigley 2017). It was previously believed that the blood-brain barrier could prevent the entry of circulating immune cells and pathogens into the brain. Nonetheless, immune cells can cross this barrier (Kivisäkk et al. 2003) and enter the CNS under pathological conditions (Obermeier, Daneman, and Ransohoff 2013). Inflammation is involved in the pathogenesis of chronic neurodegenerative diseases, including AD, MS, amyotrophic lateral sclerosis, and ASD (Spielman, Gibson, and Klegeris 2018) (Figure 2).

Prophylactic treatment with *Bifidobacterium* reduced the duration of experimental autoimmune encephalomyelitis symptoms in a mouse model of MS (Salehipour et al. 2017). Furthermore, the immune regulation of MS patients is affected by probiotics (Tankou et al. 2018). Fructooligosaccharides regulated the levels of glucagon-1 (GLP-1) in the intestine and GLP-1 receptors in the brain, improved cognition, and reduced AD in mice (Sun et al. 2019). Aspartate, glutamate, and glutamine serve as metabolic fuels for intestinal cells and, together with glycine, indirectly regulate brain function (Wu 2010). Although HPDs can potentially promote neuroinflammation, few studies have evaluated the role of microbial metabolites in brain function.

Cardiovascular diseases

Studies have shown that protein metabolites are related to CVD. L-carnitine can be oxidized to TMA by carnitine oxidoreductase (Zhu, Jameson, et al. 2014). TMA enters the portal circulation and is oxidized to trimethylamine-N-oxide (TMAO) by flavin-containing mono-oxygenase (FMO). TMAO is considered a risk factor for CVD, including atherosclerosis, thrombosis, obesity and T2DM (Tang and Hazen 2014; Wang et al. 2011; Sonnenburg and Bäckhed 2016; Tremaroli and Bäckhed 2012; Al-Obaide et al. 2017; Barrea et al. 2019; Schugar et al. 2017) (Figure 3). Studies in humans have shown that HPDs seem to result in higher levels of TMAO in urine (Rasmussen et al. 2012). Further, a previous study found that the concentrations of TAM and TMAO were high in the plasma of people at risk of CVD (Wu et al. 2019). In rodent models, the long-term consumption of carnitine significantly changed the composition of the intestinal flora and increased the plasma levels of TMAO. In addition, Apo E mice treated with TMAO or a TMAO precursor were more likely to develop atherosclerosis (Z. Wang et al. 2011). However, saturated fat is not significantly correlated with CVD (Siri-Tarino et al. 2010), which suggests that the increased risk of CVD in meat consumers is due to other factors. There is a significant dose-dependent correlation between L-carnitine and the overall risk of CVD, and L-carnitine by-products promote atherosclerosis (Koeth et al. 2013). However, few studies have evaluated the relationship between HPDs and the risk of CVD.

HPDs in athletes and the elderly

Athletes and older adults increase protein intake to meet energy requirements. The recommended protein intake for athletes engaged in moderate and high-intensity exercises is 1.0–1.6 g/kg (G. Wu 2016). The European Society for Parenteral and Enteral Nutrition and the PROT-AGE study

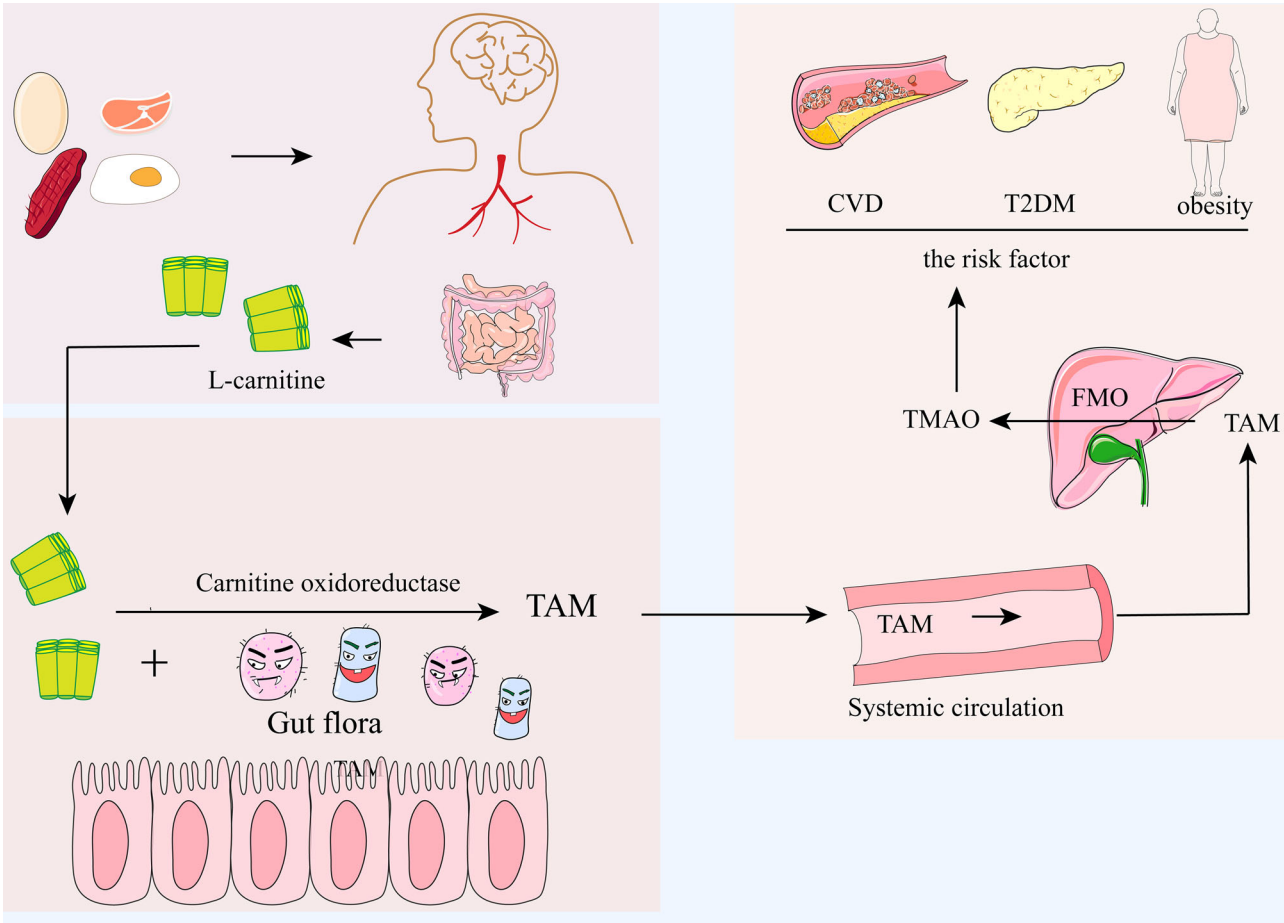

Figure 3. Protein-rich diets favor the development of cardiovascular diseases. Red meat contains large amounts of L-carnitine, which is converted to TMA by microbial activity. TMA enters the portal circulation and is oxidized to TMAO by FMO. FMO, flavin-containing mono-oxygenase; TMA, trimethylamine; TMAO, trimethylamine-N-oxide. This figure cannot be reproduced without author permission.

Table 1. Associations of high-protein diets with intestinal flora and disease risk.

High-protein diets	Gut microbiota	Results	Reference
Whey isolates and beef hydrolysate	The *Bacteroidetes phylum* ↑, *Roseburia, Blautia,* and *Bifidobacterium longum* ↓	Have a negative impact	(Koeth et al. 2019; Moreno-Pérez et al. 2018)
Red meat	*Collinsella aerofaciens* and *Clostridium spp*	The serum levels of uric acid and creatinine ↑	(Foerster et al. 2014)
Red meat	The absolute abundances of the *Clostridium coccoides,* the *Clostridium leptum, Lactobacillus spp, Parabacteroides distasonis and Ruminococcus bromii* ↑, *Ruminococcus torques* and the proportions of *Ruminococcus gnavus, Ruminococcus torques* and *Escherichia coli* ↓.	The risk of CRC ↑	(Le Leu et al. 2015)
Red meat, eggs, and dairy products	The *Verrucomicrobiaceae* family and *Enterobacteriaceae* family ↑	The risk of coronary artery disease (CAD) ↑, TMAO ↑	(Ivashkin and Kashukh 2019)
Fish	*Firmicutes* ↑, *Bacteroidetes* ↓	TMAO ↑	(Cho et al. 2017)
sardines	The *Firmicutes/Bacteroidetes* ratio ↓ and *Bacteroides-Prevotella* ↑	The adiponectin in plasma ↑,	(Balfegó et al. 2016)
meats, eggs, and cheeses	*Alistipes*, *Bilophila* and *Bacteroides* ↑, *Roseburia, Eubacterium rectale* and *Ruminococcus bromii* ↓	Bile acids ↑	(David et al. 2014)
meats, dairy products, and simple sugars	*Firmicutes* ↓ and *Bacteroidetes*↑	Bacteria-derived deoxycholic acid ↓ and acetate and butyrate in stool ↑	(Rodríguez-Morató et al. 2018)
Animal protein	*Roseburia* and *Anaerostipes* ↓	————	(Ford et al. 2020)
dairy, eggs, poultry, fish, red meat	————	TMAO ↑	(Mitchell et al. 2019)

Table 2. Effect of diet on the gut microbiome and health outcomes.

Groups at risk of disease	Dietary and lifestyle factor	Results	Reference
Intestinal-related disease	Vegetarians, vegans, and controls	Vegetarians: *Enterobacteriaceae* ↓, risk of CRC ↓;	(Zimmer et al. 2012)
	GOS and the probiotic strains *Bifidobacterium* adolescent IVS-1	Improvement in colonic permeability, *Bifidobacterium* ↑;	(Krumbeck et al. 2018)
	l-Arabinose	Composition and diversity of the gut microbiota ↑, symptoms of inflammatory bowel disease ↓;	(Li, Pan, et al. 2019)
	Goji supplementation	*Actinobacteria* ↑, *Bifidobacterial* ↑, *Lachnospiraceae-Ruminococcaceae* ↑, and *Roseburia* ↑, prevention of colitis in IL-10-deficient mice;	(Kang et al. 2018)
	Inulin-type fructans	The abundance of *Bifidobacteriaceae* and *Lachnospiraceae* ↑;	(Valcheva et al. 2019)
	Isomaltodextrin	Relative abundance of *Coprococcus* ↓, alpha-diversity, richness, and evenness in female mice ↑;	(Zhang, Hyun, et al. 2020)
	Galactoglucomannan and arabinoglucuronoxylan	Growth of *Bifidobacterium*, *Lactobacillus*, and *Bacteroides* ↑;	(La Rosa et al. 2019)
	The prebiotic Bimuno (2.8 g/day, containing 1.37 g beta-galactooligosaccharide)	Abundance of *Bifidobacterium* sequences ↑, *Bilophila wadsworthia* ↓;	(Huaman et al. 2018)
T2DM	High-fiber diet	The diversity of gut microbiota↑, HbA1c levels ↑, the partly production of glucagon-like peptide-1 ↑;	(Zhao et al. 2018)
	Metformin and AMC	*Blautia* ↑ in both groups; *Faecalibacterium* ↑ in the AMC group;	(Tong et al. 2018)
	A fiber-rich macrobiotic /control	*Faecalibacterium* ↑, fasting blood glucose ↓, *Akkermansia* and *Bacteroides* ↑, LDL-cholesterol↑, *Ruminococcus* ↑, fasting blood glucose ↓;	(Candela et al. 2016)
	Dietary inulin	Relative abundance of *Cyanobacteria* and *Bacteroides* ↑, relative abundance of *Ruminiclostridium_6* ↓;	(Li, Zhang, et al. 2019)
	Diet enriched or not with 100 g of sardines	*Firmicutes* ↓, *Escherichia coli* ↑, *Firmicutes/Bacteroidetes* ↓, *Bacteroides- Prevotella*↑;	(Balfegó et al. 2016)
	Fructooligosaccharides and galactooligosaccharides	*Bifidobacterium* ↑;	(Liu et al. 2017)
	Mannan-oligosaccharides	Improved the hypoglycemic effects of metformin in association with gut microbiota modulation ↑, relative abundance of family *Rikenellaceae* and order *Clostridiales* ↓;	(Zheng et al. 2018)
	Weighted or unweighted UniFrac and a strict vegetarian diet	Relative abundance of *Bacteroidetes* ↑;	(Kim et al. 2013)
Obesity	Interactions between dietary components (fiber, meat, and fat intake)/normal	High intake of fat and red meat ↑, alpha diversity↓;	(Stanislawski et al. 2019)
	HPDs/normal	HPDs: *Firmicutes* and *Bacteroidetes* increased amino acid degradation;	(Beaumont et al. 2017)
	Coix seed	Abundance of genera *Lactobacillus*, *Coprococcus*, and *Akkermansia* ↑;	(Liu, Li, and Zhang 2019)
	Prospective 12-week dietary intervention (see article for details)	*Firmicutes/Bacteroidetes* ratio ↓, abundance of *Prevotellaceae* ↑;	(Serena et al. 2018)
	Polysaccharides isolated from *Hirsutella sinensis*	*Parabacteroides goldsteinii* ↑, *Clostridiales* ↓;	(Hiel et al. 2019)
	29% protein, 66% fat, 5% carbohydrates	*Roseburia* ↓, SCFAs ↓, toxic metabolites (N-nitroso compounds) ↑;	(Russell et al. 2011)
	Blueberry polyphenol extract	Weight loss, *Bifidobacterium* ↑;	(Jiao et al. 2019)
	Mannan-oligosaccharide	Body weight ↓, serum lipids and insulin resistance ↓, *Firmicutes/Bacteroidetes* ratio ↓;	(Wang et al. 2018)
	Physical activity	*Akkermansia* ↑, gut microbial diversity ↑;	(Clarke et al. 2014)
	Galactooligosaccharide mixture supplementation	*Bifidobacteria* ↑, no significant change in obesity parameters;	(Vulevic et al. 2013)
CNS	Intermittent fasting	Pro-inflammatory T cells ↓, *Lactobacilli* ↑;	(Cignarella et al. 2018)
	B-GOS prebiotic intervention	Abundance of *Bifidobacterium* ↑;	(Grimaldi et al. 2018)
	Probiotic VSL3	*Lactobacillus*, *Streptococcus*, and *Bifidobacterium* ↑;	(Tankou et al. 2018)
	Inulin-type fructans	*Bifidobacterium* ↑;	(Vandeputte et al. 2017)
	Prebiotics 3′ sialyllactose and 6′ sialyllactose	*Firmicutes* and *Cyanobacteria* ↓, *Bacteroidetes* ↑;	(Tarr et al. 2015)
	Schisandra chinensis	Relative *Bacteroidetes* to *Firmicutes* ratio ↑;	(Yan et al. 2021)
	Vivomixx	Abundance of *Bacteroidetes*, *Actinobacteria*, *Tenericutes* ↑;	(Mestre et al. 2020)
CVD	Dietary fiber intervention/no intervention	Abundance of *Bifidobacterium* and *Lactobacillus* ↑;	(So et al. 2018)
	Prebiotic inulin or probiotic *Lactobacillus*	Plasma TMAO level and TMAO to TMA ratio ↓, *Firmicutes* to *Bacteroidetes* ratio ↓, abundance of *Lactobacillus* and *Akkermansia* ↑;	(Hsu et al. 2019)
	High-flavonoid or low flavonoid diets	*C. leptum-R. bromii/flavefaciens*, *Bifidobacterium* and *Bacteroides/Prevotella* ↑;	(Klinder et al. 2016)
	Pterostilbene	Vascular cell adhesion molecule 1 ↓, abundance of *Bacteroides* ↑;	(Koh et al. 2019)
	Olive pomace-enriched biscuit	*Bifidobacteria* abundance ↑;	(Conterno et al. 2019)
	Xanthohumol derivatives		(Zhang, Bobe, et al. 2020)

(*continued*)

Table 2. Continued.

Groups at risk of disease	Dietary and lifestyle factor	Results	Reference
		Abundance of *Bacteroidetes* and *Tenericutes* ↓, alters bile acid metabolism and reduces inflammation;	
	Diet with and without seafood	Diet without seafood: TMA ↓, relative abundance of *Clostridium cluster IV* ↓, *Firmicutes/Bacteroidetes* ratio ↑;	(Schmedes et al. 2019)
	Fermented green tea extract	Proportion of the phylum *Firmicutes* ↓;	(Seo et al. 2017)
	Moderate-intensity Exercise	Relative abundance of *Butyricimonas* and *Akkermansia* ↑;	(Liu et al. 2017)
	A maize-based whole grain breakfast	The levels of fecal *Bifidobacterium* ↑;	(Carvalho-Wells et al. 2010)

CRC, colorectal cancer; GOS, galactooligosaccharides; A1c, hemoglobin A1C; AMC, a formula containing the herb *Coptis chinensis*; HPDs, high-protein diets; probiotic; VSL3, a cocktail of eight bacteria; SCFAs, short-chain fatty acids; TMAO, trimethylamine oxide; TMA, trimethylamine; Vivomixx, multi-probiotic mixture.

recommends the daily consumption of 1.0–1.2 g/kg by older adults to prevent sarcopenia (age-related loss of muscle mass) (Deutz et al. 2014; Bauer et al. 2013).

Athletes

Individuals engaged in regular, intense, or prolonged exercises consume HPDs and protein and AA supplements to meet energy requirements (Kårlund et al. 2019; Bianco et al. 2011; Gannon Schnuck and Vaughan 2018). HPDs increase muscle mass, particularly with strength training. Moreover, high protein intake (usually 30% or more of total daily energy) is recommended during energy-restricted weight loss. There is growing evidence that high-protein low-energy diets can help achieve weight and fat loss in overweight and obese people. HPDs are also used to recover from sports injuries. High protein intake ameliorates the detrimental effects of high-eccentric strength training, including a temporary decrease in muscle force production, soreness, and changes in muscle protein concentration (Howatson and Van Someren 2008). However, excess protein consumption may lead to intestinal inflammation, and fermentation products can potentially cause immune disorders (Clark and Mach 2016). In addition, protein requirements can vary depending on individual exercise intensity and metabolic status. Therefore, dietary interventions should consider individual differences in intestinal homeostasis (Kårlund et al.2019).

The appropriate intake of proteins is crucial for athletes, and AA malnutrition can impact bone and muscle health (Ilan et al. 2000). Athletic performance is strongly dependent on bone health, and healthy bones reduce the risk of sports injuries (Sale and Elliott-Sale 2019). HPDs improve calcium retention and absorption when the calcium concentration obtained from other foods is insufficient (Kerstetter, Kenny, and Insogna 2011) but are detrimental to bone health by promoting bone mineral loss when the calcium concentration obtained from other foods is normal (Sale and Elliott-Sale 2019). Considering athletes' demand for protein, athletes need to increase the diversity of their intestinal flora and proportion of probiotics to adapt to the individual's demand for more protein metabolism (Marttinen et al. 2020; Wosinska et al. 2019; Jang et al. 2019).

The consumption of probiotics such as Bifidobacterium improves intestinal health and the ingestion of probiotic yogurt improved aerobic performance in young female swimmers (Salarkia et al. 2013). A study showed that a 14-week probiotic supplementation normalized the concentrations of zonulin (a marker of intestinal permeability) in the stool and reduced protein oxidation induced by tumor necrosis factor in male athletes (Lamprecht et al. 2012). Therefore, HPDs can reduce the production of toxic metabolites, and probiotics can regulate the intestinal flora. However, among individuals on HPDs, the risk of intestinal inflammation is lower in athletes than in sedentary people because exercise increases gut microbial diversity (Clarke et al. 2014).

Older adults

Dietary protein is crucial to meet energy requirements and maintain skeletal muscle function in elderly individuals. Muscle function status is closely related to the quality of life in this population. Sarcopenia usually begins at the age of 30 (Welch 2014) and is caused by protein deficiency, which is attributed to a decrease in chewing ability, taste sensitivity, appetite, and digestion. A study in obese adults older than 70 years showed that HPDs reduced muscle loss and facilitated moderate weight loss but did not improve cardiometabolic health and systemic inflammation (Wright et al. 2018). Microbial abundance is highly affected by drug treatment, disease status, and lifestyle. During aging, physical deterioration is increased, whereas protein absorption and gut microbial resilience and richness are decreased (Ticinesi et al. 2017), leading to inflammation (Dillon 2013). Aging associated with chronic inflammation changes the diversity of the intestinal microbiota, leading to protein synthesis disorders in skeletal muscle. Previous studies have shown a positive relationship between protein intake and muscle strength and mass (Isanejad et al. 2016; Landi et al. 2017; Houston et al. 2008).

A study showed that in healthy elderly people, short-term intake of HPDs (2.0 g protein/kg/day) does not show obvious toxic effects on the kidneys, although it increases the acid content in the urine. In young people, exposure to HPDs for two months did not show adverse effects on kidney metabolism (Wagner et al. 2007). The use of high-protein low-carbohydrate diets for weight loss has always been controversial. A study showed that short-term high-protein low-carbohydrate diets can appropriately reduce weight and improve blood quality. However, when it lasts for more than six months, a high-protein low-carbohydrate diet has a higher risk of disease than a traditional diet (Cunningham and Hyson 2006). In overweight and obese elderly people, a 12-week HPD (2.0 g protein/kg/day) had no significant effect

on muscle composition, cardiometabolic health, and systemic inflammation (Wright et al. 2018). In addition, a 10-week HPD (1.3 g protein/kg/day) has no significant effect on the fat free mass (FFM) of obese elder adults, but FFM increased significantly when the HPD was combined with exercise (Verreijen et al. 2017).

Probiotics increase microbial abundance in the intestine and increase protein fermentation (Jäger et al. 2018; Maathuis, Keller, and Farmer 2010), which may reduce skeletal muscle resistance in older adults due to protein anabolism. Butyrate improves muscle atrophy in mice. Prebiotics favor the production of SCFAs, which are used as an energy source by the host (den Besten et al. 2013), and reduction of the produced SCFAs in the intestine may lead to reduced skeletal muscle resistance from protein anabolism in elderly individuals (Yan et al. 2016; Frampton et al. 2020). A metagenomic study found that aging was associated with the deletion of genes involved in SCFA production (Rampelli et al. 2013). Therefore, prebiotics and probiotics maintain protein homeostasis, especially in the elderly population.

Conclusions

This study explored the relationship between HPDs and high-risk groups, including athletes and the elderly, who need to increase protein intake to maintain muscle function. In addition, HPDs are associated with intestinal, metabolic, CNS, and CVD. HPDs are often also related to changes in certain intestinal flora, as shown in Table 1. Studies have shown that long-term HPDs may increase the risk of these diseases by increasing the production of toxic metabolites by colonic bacteria. Short-term HPDs have little effect on the metabolism of healthy people younger than 65 years but improve muscle function in the elderly. However, excessive protein intake by the elderly reduces gut microbial diversity and produces toxic metabolites. Disease risk is not increased in athletes who consume HPDs to improve muscle function, possibly due to the benefits of regular exercise. In contrast, the consumption of red meat increases disease risk compared with other protein sources. Nonetheless, few studies have assessed the effects of protein diets and the gut microbiome on health. This review assessed the effects of HPDs on health outcomes. Scientific evidence indicates that physical activity and the intake of natural substances, prebiotics, and probiotics improve microbial dysbiosis and help prevent and treat diseases (Table 2). Bioactive substances including plant-derived active peptides also show positive effects on the intestinal flora (Cui, Lin, and Liang 2020; Ashaolu 2020). A peptide of eight amino acids from rice bran has been shown by our laboratory to have antioxidant and anti-aging effects on cells and mice (Wang et al. 2020; Liang et al. 2018). Its effects on the intestinal flora linked with antiaging and human health need to be further explored. Some intervention studies have shown that prebiotics and probiotics do not change the structure and composition of the intestinal flora. The development of treatment formulations containing both appropriate probiotics and prebiotics may enhance the effects of host probiotics (Bomba et al. 2002). Further studies are necessary to elucidate the effect of prebiotics, probiotics, and microbial metabolites on host physiology. Moreover, understanding the mechanism of action of probiotics paves the way for using microorganisms to treat human diseases and reduce the adverse effects of HPDs.

Disclosure statement

The authors declare that there is no financial conflict of interest.

Funding

This work was supported by funding from the Natural Science Foundation of Hunan Province (No. 2020JJ4138), Hunan Furong Scholars Program, Huxiang Youth Talents Supporting Program (No. 2016RS3033), National Natural Science Foundation of China (No. 31771918), Scientific Research Foundation of Hunan Provincial Education Department (No. 18A160), and Grain-oil Process and Quality Control 2011 Collaborative and Innovative Grant from Hunan Province.

References

Adamczyk-Sowa, M., A. Medrek, P. Madej, W. Michlicka, and P. Dobrakowski. 2017. Does the gut microbiota influence immunity and inflammation in multiple sclerosis pathophysiology? *Journal of Immunology Research* 2017:7904821. doi: 10.1155/2017/7904821.

Agranoff, B. W., and D. Goldberg. 1974. Diet and the geographical distribution of multiple sclerosis. *The Lancet* 2 (7888):1061–6. doi: 10.1016/S0140-6736(74)92163-1.

Al-Obaide, MaI, R. Singh, P. Datta, K. A. Rewers-Felkins, M. V. Salguero, I. Al-Obaidi, K. R. Kottapalli, and T. L. Vasylyeva. 2017. Gut microbiota-dependent trimethylamine-n-oxide and serum biomarkers in patients with t2dm and advanced ckd. *Journal of Clinical Medicine* 6 (9).86. doi: 10.3390/jcm60900:.

Ashaolu, T. J. 2020. Soy bioactive peptides and the gut microbiota modulation. *Applied Microbiology and Biotechnology* 104 (21): 9009–17. doi: 10.1007/s00253-020-10799-2.

Avila, E. T. P., T. Da Rosa Lima, R. A. Tibana, P. C. De Almeida, G. A. Fraga, M. De Souza Sena, L. F. P. Corona, J. W. Navalta, S. Rezaei, M. Ghayomzadeh, et al. 2018. Effects of high-protein diet containing isolated whey protein in rats submitted to resistance training of aquatic jumps. *Nutrition (Burbank, Los Angeles County, Calif.)* 53:85–94. doi: 10.1016/j.nut.2018.01.018.

Balfegó, M., S. Canivell, F. A. Hanzu, A. Sala-Vila, M. Martínez-Medina, S. Murillo, T. Mur, E. G. Ruano, F. Linares, N. Porras, et al. 2016. Effects of sardine-enriched diet on metabolic control, inflammation and gut microbiota in drug-naïve patients with type 2 diabetes: A pilot randomized trial. *Lipids in Health and Disease* 15: 78. doi: 10.1186/s12944-016-0245-0.

Barrea, L., G. Muscogiuri, G. Annunziata, D. Laudisio, G. De Alteriis, G. C. Tenore, A. Colao, and S. Savastano. 2019. A new light on vitamin D in obesity: A novel association with trimethylamine-n-oxide (TMAO). *Nutrients* 11 (6):1310. doi: 10.3390/nu11061310.

Bauer, J., G. Biolo, T. Cederholm, M. Cesari, A. J. Cruz-Jentoft, J. E. Morley, S. Phillips, C. Sieber, P. Stehle, D. Teta, et al. 2013. Evidence-based recommendations for optimal dietary protein intake in older people: A position paper from the prot-age study group. *Journal of the American Medical Directors Association* 14 (8):542–59. doi: 10.1016/j.jamda.2013.05.021.

Beaumont, M., K. J. Portune, N. Steuer, A. Lan, V. Cerrudo, M. Audebert, F. Dumont, G. Mancano, N. Khodorova, M. Andriamihaja, et al. 2017. Quantity and source of dietary protein influence metabolite production by gut microbiota and rectal

mucosa gene expression: A randomized, parallel, double-blind trial in overweight humans. *The American Journal of Clinical Nutrition* 106 (4):1005–19. doi: 10.3945/ajcn.117.158816.

Bianco, A., C. Mammina, A. Paoli, M. Bellafiore, G. Battaglia, G. Caramazza, A. Palma, and M. Jemni. 2011. Protein supplementation in strength and conditioning adepts: Knowledge, dietary behavior and practice in Palermo, Italy. *Journal of the International Society of Sports Nutrition* 8 (1):25. doi: 10.1186/1550-2783-8-25.

Bomba, A., R. Nemcová, D. Mudroňová, and P. Guba. 2002. The possibilities of potentiating the efficacy of probiotics. *Trends in Food Science & Technology* 13 (4):121–6. doi: 10.1016/S0924-2244(02)00129-2.

Bonaz, B.,. T. Bazin, and S. Pellissier. 2018. The vagus nerve at the interface of the microbiota-gut-brain axis. *Frontiers in Neuroscience* 12:49. doi: 10.3389/fnins.2018.00049.

Campos-Nonato, I., L. Hernandez, and S. Barquera. 2017. Effect of a high-protein diet versus standard-protein diet on weight loss and biomarkers of metabolic syndrome: A randomized clinical trial. *Obesity Facts* 10 (3):238–51. doi: 10.1159/000471485.

Candela, M., E. Biagi, M. Soverini, C. Consolandi, S. Quercia, M. Severgnini, C. Peano, S. Turroni, S. Rampelli, P. Pozzilli, et al. 2016. Modulation of gut microbiota dysbioses in type 2 diabetic patients by macrobiotic ma-pi 2 diet. *The British Journal of Nutrition* 116 (1):80–93. doi: 10.1017/s0007114516001045.

Carvalho-Wells, A. L., K. Helmolz, C. Nodet, C. Molzer, C. Leonard, B. Mckevith, F. Thielecke, K. G. Jackson, and K. M. Tuohy. 2010. Determination of the in vivo prebiotic potential of a maize-based whole grain breakfast cereal: A human feeding study. *The British Journal of Nutrition* 104 (9):1353–6. doi: 10.1017/s0007114510002084.

Cho, C. E., S. Taesuwan, O. V. Malysheva, E. Bender, N. F. Tulchinsky, J. Yan, J. L. Sutter, and M. A. Caudill. 2017. Trimethylamine-n-oxide (tmao) response to animal source foods varies among healthy young men and is influenced by their gut microbiota composition: A randomized controlled trial. *Molecular Nutrition & Food Research* 61 (1):1770016. doi: 10.1002/mnfr.201600324.

Cignarella, F., C. Cantoni, L. Ghezzi, A. Salter, Y. Dorsett, L. Chen, D. Phillips, G. M. Weinstock, L. Fontana, A. H. Cross, et al. 2018. Intermittent fasting confers protection in CNS autoimmunity by altering the gut microbiota. *Cell Metabolism* 27 (6):1222–35.e6. doi: 10.1016/j.cmet.2018.05.006.

Clark, A., and N. Mach. 2016. Exercise-induced stress behavior, gut-microbiota-brain axis and diet: A systematic review for athletes. *Journal of the International Society of Sports Nutrition* 13:43. doi: 10.1186/s12970-016-0155-6.

Clarke, S. F., E. F. Murphy, O. O'sullivan, A. J. Lucey, M. Humphreys, A. Hogan, P. Hayes, M. O'reilly, I. B. Jeffery, R. Wood-Martin, et al. 2014. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut* 63 (12):1913–20. doi: 10.1136/gutjnl-2013-306541.

Clements, S. J., and S. R. Carding. 2018. Diet, the intestinal microbiota, and immune health in aging. *Critical Reviews in Food Science and Nutrition* 58 (4):651–61. doi: 10.1080/10408398.2016.1211086.

Conterno, L., F. Martinelli, M. Tamburini, F. Fava, A. Mancini, M. Sordo, M. Pindo, S. Martens, D. Masuero, U. Vrhovsek, et al. 2019. Measuring the impact of olive pomace enriched biscuits on the gut microbiota and its metabolic activity in mildly hypercholesterolaemic subjects. *European Journal of Nutrition* 58 (1):63–81. doi: 10.1007/s00394-017-1572-2.

Cryan, J. F., K. J. O'riordan, C. S. M. Cowan, K. V. Sandhu, T. F. S. Bastiaanssen, M. Boehme, M. G. Codagnone, S. Cussotto, C. Fulling, A. V. Golubeva, et al. 2019. The microbiota-gut-brain axis. *Physiological Reviews* 99 (4):1877–2013. doi: 10.1152/physrev.00018.2018.

Cuenca-Sánchez, M., D. Navas-Carrillo, and E. Orenes-Piñero. 2015. Controversies surrounding high-protein diet intake: Satiating effect and kidney and bone health. *Advances in Nutrition (Bethesda, Md.)* 6 (3):260–6. doi: 10.3945/an.114.007716.

Cui, X., Q. Lin, and Y. Liang. 2020. Plant-derived antioxidants protect the nervous system from aging by inhibiting oxidative stress. *Frontiers in Aging Neuroscience* 12:209. doi: 10.3389/fnagi.2020.00209.

Cunningham, W., and D. Hyson. 2006. The skinny on high-protein, low-carbohydrate diets. *Preventive Cardiology* 9 (3):166–73. doi: 10.1111/j.1520-037X.2006.04853.x.

David, L. A., C. F. Maurice, R. N. Carmody, D. B. Gootenberg, J. E. Button, B. E. Wolfe, A. V. Ling, A. S. Devlin, Y. Varma, M. A. Fischbach, et al. 2014. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 505 (7484):559–63. doi: 10.1038/nature12820.

Den Besten, G., K. Lange, R. Havinga, T. H. Van Dijk, A. Gerding, K. Van Eunen, M. Müller, A. K. Groen, G. J. Hooiveld, B. M. Bakker, et al. 2013. Gut-derived short-chain fatty acids are vividly assimilated into host carbohydrates and lipids. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 305 (12):G900–10. doi: 10.1152/ajpgi.00265.2013.

Deutz, N. E., J. M. Bauer, R. Barazzoni, G. Biolo, Y. Boirie, A. Bosy-Westphal, T. Cederholm, A. Cruz-Jentoft, Z. Krznariç, K. S. Nair, et al. 2014. Protein intake and exercise for optimal muscle function with aging: Recommendations from the espen expert group. *Clinical Nutrition (Edinburgh, Scotland)* 33 (6):929–36. doi: 10.1016/j.clnu.2014.04.007.

Diether, N. E., and B. P. Willing. 2019. Microbial fermentation of dietary protein: An important factor in diet¯microbe¯host interaction. *Microorganisms* 7 (1):19. doi: 10.3390/microorganisms7010019.

Dillon, E. L. 2013. Nutritionally essential amino acids and metabolic signaling in aging. *Amino Acids* 45 (3):431–41. doi: 10.1007/s00726-012-1438-0.

Foerster, J., G. Maskarinec, N. Reichardt, A. Tett, A. Narbad, M. Blaut, and H. Boeing. 2014. The influence of whole grain products and red meat on intestinal microbiota composition in normal weight adults: A randomized crossover intervention trial. *PLoS One* 9 (10):e109606. doi: 10.1371/journal.pone.0109606.

Ford, A. L., V. Nagulesapillai, A. Piano, J. Auger, S.-A. Girard, M. Christman, T. A. Tompkins, and W. J. Dahl. 2020. Microbiota stability and gastrointestinal tolerance in response to a high-protein diet with and without a prebiotic, probiotic, and synbiotic: A randomized, double-blind, placebo-controlled trial in older women. *Journal of the Academy of Nutrition and Dietetics* 120 (4):500–16.e10. doi: 10.1016/j.jand.2019.12.009.

Frampton, J., K. G. Murphy, G. Frost, and E. S. Chambers. 2020. Short-chain fatty acids as potential regulators of skeletal muscle metabolism and function. *Nature Metabolism* 2 (9):840–8. doi: 10.1038/s42255-020-0188-7.

Fuller, M. 2012. Determination of protein and amino acid digestibility in foods including implications of gut microbial amino acid synthesis. *The British Journal of Nutrition* 108 Suppl 2 (Suppl 2):S238–S46. doi: 10.1017/s0007114512002279.

Gannon, N. P., J. K. Schnuck, and R. A. Vaughan. 2018. Bcaa metabolism and insulin sensitivity - dysregulated by metabolic status? *Molecular Nutrition & Food Research* 62 (6):e1700756. doi: 10.1002/mnfr.201700756.

Grandl, G., and C. Wolfrum. 2018. Hemostasis, endothelial stress, inflammation, and the metabolic syndrome. *Seminars in Immunopathology* 40 (2):215–24. doi: 10.1007/s00281-017-0666-5.

Grenham, S., G. Clarke, J. F. Cryan, and T. G. Dinan. 2011. Brain-gut-microbe communication in health and disease. *Frontiers in Physiology* 2:. : 10.3389/fphys.2011.00094. doi: 10.3389/fphys.2011.00094.

Grimaldi, R., G. R. Gibson, J. Vulevic, N. Giallourou, J. L. Castro-Mejía, L. H. Hansen, E. L. Gibson, D. S. Nielsen, and A. Costabile. 2018. A prebiotic intervention study in children with autism spectrum disorders (ASDs). *Microbiome* 6 (1):133. doi: 10.1186/s40168-018-0523-3.

Hashimoto, T., T. Perlot, A. Rehman, J. Trichereau, H. Ishiguro, M. Paolino, V. Sigl, T. Hanada, R. Hanada, S. Lipinski, et al. 2012. Ace2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 487 (7408):477–81. doi: 10.1038/nature11228.

Hemmings, W. A., and E. W. Williams. 1978. Transport of large breakdown products of dietary protein through the gut wall. *Gut* 19 (8): 715–23. doi: 10.1136/gut.19.8.715.

Hiel, S., L. B. Bindels, B. D. Pachikian, G. Kalala, V. Broers, G. Zamariola, B. P. I. Chang, B. Kambashi, J. Rodriguez, P. D. Cani, et al. 2019. Effects of a diet based on inulin-rich vegetables on gut health and nutritional behavior in healthy humans. *The American Journal of Clinical Nutrition* 109 (6):1683–95. doi: 10.1093/ajcn/nqz001.

Houston, D. K., B. J. Nicklas, J. Ding, T. B. Harris, F. A. Tylavsky, A. B. Newman, J. S. Lee, N. R. Sahyoun, M. Visser, and S. B. Kritchevsky. 2008. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: The health, aging, and body composition (health ABC) study. *The American Journal of Clinical Nutrition* 87 (1):150–5. doi: 10.1093/ajcn/87.1.150.

Howatson, G., and K. A. Van Someren. 2008. The prevention and treatment of exercise-induced muscle damage. *Sports Medicine (Auckland, N.Z.)* 38 (6):483–503. doi: 10.2165/00007256-200838060-00004.

Hsu, C. N., C. Y. Hou, J. Y. H. Chan, C. T. Lee, and Y. L. Tain. 2019. Hypertension programmed by perinatal high-fat diet: Effect of maternal gut microbiota-targeted therapy. *Nutrients* 11 (12)2908. doi: 10.3390/nu1112:.

Huaman, J. W., M. Mego, C. Manichanh, N. Cañellas, D. Cañueto, H. Segurola, M. Jansana, C. Malagelada, A. Accarino, J. Vulevic, et al. 2018. Effects of prebiotics vs a diet low in fodmaps in patients with functional gut disorders. *Gastroenterology* 155 (4):1004–7. doi: 10.1053/j.gastro.2018.06.045.

Hussain, M., M. Umair Ijaz, M. I. Ahmad, I. A. Khan, S. A. Brohi, A. U. Shah, K. I. Shinwari, D. Zhao, X. Xu, G. Zhou, et al. 2019. Meat proteins in a high-fat diet have a substantial impact on intestinal barriers through mucus layer and tight junction protein suppression in c57bl/6j mice. *Food & Function* 10 (10):6903–14. doi: 10.1039/c9fo01760g.

Ilan, Y., T. Sobol, O. Sasson, Y. Ashur, and E. M. Berry. 2000. A balanced 5:1 carbohydrate: Protein diet: A new method for supplementing protein to patients with chronic liver disease. *Journal of Gastroenterology and Hepatology* 15 (12):1436–41. doi: 10.1046/j.1440-1746.2000.02281.x.

Isanejad, M., J. Mursu, J. Sirola, H. Kröger, T. Rikkonen, M. Tuppurainen, and A. T. Erkkilä. 2016. Dietary protein intake is associated with better physical function and muscle strength among elderly women. *British Journal of Nutrition* 115 (7):1281–91. doi: 10.1017/S000711451600012X.

Ivashkin, V. T., and Y. A. Kashukh. 2019. Impact of l-carnitine and phosphatidylcholine containing products on the proatherogenic metabolite tmao production and gut microbiome changes in patients with coronary artery disease. *Voprosy Pitaniia* 88 (4):25–33. doi: 10.24411/0042-8833-2019-10038.

Jäger, R., M. Purpura, S. Farmer, H. A. Cash, and D. Keller. 2018. Probiotic *Bacillus coagulans* gbi-30, 6086 improves protein absorption and utilization. *Probiotics and Antimicrobial Proteins* 10 (4): 611–5. doi: 10.1007/s12602-017-9354-y.

Jain, S. K., R. Bull, J. L. Rains, P. F. Bass, S. N. Levine, S. Reddy, R. Mcvie, and J. A. Bocchini. 2010. Low levels of hydrogen sulfide in the blood of diabetes patients and streptozotocin-treated rats causes vascular inflammation? *Antioxidants & Redox Signaling* 12 (11): 1333–7. doi: 10.1089/ars.2009.2956.

Jang, L. G., G. Choi, S. W. Kim, B. Y. Kim, S. Lee, and H. Park. 2019. The combination of sport and sport-specific diet is associated with characteristics of gut microbiota: An observational study. *Journal of the International Society of Sports Nutrition* 16 (1):21. doi: 10.1186/s12970-019-0290-y.

Jiao, X., Y. Wang, Y. Lin, Y. Lang, E. Li, X. Zhang, Q. Zhang, Y. Feng, X. Meng, and B. Li. 2019. Blueberry polyphenols extract as a potential prebiotic with anti-obesity effects on c57bl/6 j mice by modulating the gut microbiota. *The Journal of Nutritional Biochemistry* 64: 88–100. doi: 10.1016/j.jnutbio.2018.07.008.

Kang, Y., G. Yang, S. Zhang, C. F. Ross, and M. J. Zhu. 2018. Goji berry modulates gut microbiota and alleviates colitis in il-10-deficient mice. *Molecular Nutrition & Food Research* 62 (22): e1800535. doi: 10.1002/mnfr.201800535.

Karlsson, C. L. J., J. Onnerfält, J. Xu, G. Molin, S. Ahrné, and K. Thorngren-Jerneck. 2012. The microbiota of the gut in preschool children with normal and excessive body weight. *Obesity (Silver Spring, Md.)* 20 (11):2257–61. doi: 10.1038/oby.2012.110.

Kårlund, A., C. Gómez-Gallego, A. M. Turpeinen, O. M. Palo-Oja, H. El-Nezami, and M. Kolehmainen. 2019. Protein supplements and their relation with nutrition, microbiota composition and health: Is more protein always better for sportspeople. ? *Nutrients* 11 (4):829. doi: 10.3390/nu11040829.

Kaur, H., C. Das, and S. S. Mande. 2017. In silico analysis of putrefaction pathways in bacteria and its implication in colorectal cancer. *Front Microbiol* 8:2166 doi: 10.3389/fmicb.2017.02166.

Kerstetter, J. E., A. M. Kenny, and K. L. Insogna. 2011. Dietary protein and skeletal health: A review of recent human research. *Curr Opin Lipidol* 22 (1):16–20. doi: 10.1097/MOL.0b013e3283419441.

Kim, M. S., S. S. Hwang, E. J. Park, and J. W. Bae. 2013. Strict vegetarian diet improves the risk factors associated with metabolic diseases by modulating gut microbiota and reducing intestinal inflammation. *Environmental Microbiology Reports* 5 (5):765–75. doi: 10.1111/1758-2229.12079.

Kivisäkk, P., D. J. Mahad, M. K. Callahan, C. Trebst, B. Tucky, T. Wei, L. Wu, E. S. Baekkevold, H. Lassmann, S. M. Staugaitis, et al. 2003. Human cerebrospinal fluid central memory cd4+ t cells: Evidence for trafficking through choroid plexus and meninges via p-selectin. *Proceedings of the National Academy of Sciences of the United States of America* 100 (14):8389–94. doi: 10.1073/pnas.1433000100.

Klinder, A., Q. Shen, S. Heppel, J. A. Lovegrove, I. Rowland, and K. M. Tuohy. 2016. Impact of increasing fruit and vegetables and flavonoid intake on the human gut microbiota. *Food & Function* 7 (4): 1788–96. doi: 10.1039/c5fo01096a.

Koeth, R. A., B. R. Lam-Galvez, J. Kirsop, Z. Wang, B. S. Levison, X. Gu, M. F. Copeland, D. Bartlett, D. B. Cody, H. J. Dai, et al. 2019. L-carnitine in omnivorous diets induces an atherogenic gut microbial pathway in humans. *The Journal of Clinical Investigation* 129 (1):373–87. doi: 10.1172/jci94601.

Koeth, R. A., Z. Wang, B. S. Levison, J. A. Buffa, E. Org, B. T. Sheehy, E. B. Britt, X. Fu, Y. Wu, L. Li, et al. 2013. Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature Medicine* 19 (5):576–85. doi: 10.1038/nm.3145.

Koh, Y. C., S. Li, P. Y. Chen, J. C. Wu, N. Kalyanam, C. T. Ho, and M. H. Pan. 2019. Prevention of vascular inflammation by pterostilbene via trimethylamine-n-oxide reduction and mechanism of microbiota regulation. *Molecular Nutrition & Food Research* 63 (20): e1900514. doi: 10.1002/mnfr.201900514.

Koppe, L., N. J. Pillon, R. E. Vella, M. L. Croze, C. C. Pelletier, S. Chambert, Z. Massy, G. Glorieux, R. Vanholder, Y. Dugenet, et al. 2013. P-cresyl sulfate promotes insulin resistance associated with ckd. *Journal of the American Society of Nephrology: JASN* 24 (1): 88–99. doi: 10.1681/asn.2012050503.

Krumbeck, J. A., H. E. Rasmussen, R. W. Hutkins, J. Clarke, K. Shawron, A. Keshavarzian, and J. Walter. 2018. Probiotic bifidobacterium strains and galactooligosaccharides improve intestinal barrier function in obese adults but show no synergism when used together as synbiotics. *Microbiome* 6 (1):121. doi: 10.1186/s40168-018-0494-4.

La Rosa, S. L., V. Kachrimanidou, F. Buffetto, P. B. Pope, N. A. Pudlo, E. C. Martens, R. A. Rastall, G. R. Gibson, and B. Westereng. 2019. Wood-derived dietary fibers promote beneficial human gut microbiota. *mSphere* 4 (1):e00554-18. doi: 10.1128/mSphere.00554-18.

Lamprecht, M., S. Bogner, G. Schippinger, K. Steinbauer, F. Fankhauser, S. Hallstroem, B. Schuetz, and J. F. Greilberger. 2012. Probiotic supplementation affects markers of intestinal barrier, oxidation, and inflammation in trained men; a randomized, double-blinded, placebo-controlled trial. *Journal of the International Society of Sports Nutrition* 9 (1):45. doi: 10.1186/1550-2783-9-45.

Landi, F., R. Calvani, M. Tosato, A. M. Martone, A. Picca, E. Ortolani, G. Savera, S. Salini, M. Ramaschi, R. Bernabei, et al. 2017. Animal-derived protein consumption is associated with muscle mass and strength in community-dwellers: Results from the Milan Expo

Survey. *The Journal of Nutrition, Health & Aging* 21 (9):1050–6. doi: 10.1007/s12603-017-0974-4.

Larsen, N., F. K. Vogensen, F. W. J. Van Den Berg, D. S. Nielsen, A. S. Andreasen, B. K. Pedersen, W. A. Al-Soud, S. J. Sørensen, L. H. Hansen, and M. Jakobsen. 2010. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 5 (2):e9085. doi: 10.1371/journal.pone.0009085.

Le Leu, R. K., J. M. Winter, C. T. Christophersen, G. P. Young, K. J. Humphreys, Y. Hu, S. W. Gratz, R. B. Miller, D. L. Topping, A. R. Bird, et al. 2015. Butyrylated starch intake can prevent red meat-induced o6-methyl-2-deoxyguanosine adducts in human rectal tissue: A randomised clinical trial. *British Journal of Nutrition* 114 (2): 220–30. doi: 10.1017/S0007114515001750.

Li, K., L. Zhang, J. Xue, X. Yang, X. Dong, L. Sha, H. Lei, X. Zhang, L. Zhu, Z. Wang, et al. 2019. Dietary inulin alleviates diverse stages of type 2 diabetes mellitus via anti-inflammation and modulating gut microbiota in db/db mice. *Food & Function* 10 (4):1915–27. doi: 10.1039/c8fo02265h.

Li, Y., H. Pan, J. X. Liu, T. Li, S. Liu, W. Shi, C. Sun, M. Fan, L. Xue, Y. Wang, et al. 2019. L-arabinose inhibits colitis by modulating gut microbiota in mice. *Journal of Agricultural and Food Chemistry* 67 (48):13299–306. doi: 10.1021/acs.jafc.9b05829.

Liang, Y., Q. Lin, P. Huang, Y. Wang, J. Li, L. Zhang, and J. Cao. 2018. Rice bioactive peptide binding with tlr4 to overcome ho-induced injury in human umbilical vein endothelial cells through nf-κb signaling. *Journal of Agricultural and Food Chemistry* 66 (2): 440–8. doi: 10.1021/acs.jafc.7b04036.

Liu, F., P. Li, M. Chen, Y. Luo, M. Prabhakar, H. Zheng, Y. He, Q. Qi, H. Long, Y. Zhang, et al. 2017. Fructooligosaccharide (fos) and galactooligosaccharide (gos) increase bifidobacterium but reduce butyrate producing bacteria with adverse glycemic metabolism in healthy young population. *Scientific Reports* 7 (1):11789. doi: 10.1038/s41598-017-10722-2.

Liu, S., F. Li, and X. Zhang. 2019. Structural modulation of gut microbiota reveals coix seed contributes to weight loss in mice. *Applied Microbiology and Biotechnology* 103 (13):5311–21. doi: 10.1007/s00253-019-09786-z.

Liu, Z., H. Y. Liu, H. Zhou, Q. Zhan, W. Lai, Q. Zeng, H. Ren, and D. Xu. 2017. Moderate-intensity exercise affects gut microbiome composition and influences cardiac function in myocardial infarction mice. *Frontiers in Microbiology* 8:1687. doi: 10.3389/fmicb.2017.01687.

Maathuis, A. J., D. Keller, and S. Farmer. 2010. Survival and metabolic activity of the ganedenbc30 strain of *Bacillus coagulans* in a dynamic in vitro model of the stomach and small intestine. *Benef Microbes* 1 (1):31–6. doi: 10.3920/BM2009.0009.

Madsen, L., L. M. Pedersen, B. Liaset, T. Ma, R. K. Petersen, S. Van Den Berg, J. Pan, K. Müller-Decker, E. D. Dülsner, R. Kleemann, et al. 2008. Camp-dependent signaling regulates the adipogenic effect of n-6 polyunsaturated fatty acids. *The Journal of Biological Chemistry* 283 (11):7196–205. doi: 10.1074/jbc.M707775200.

Marttinen, M., R. Ala-Jaakkola, A. Laitila, and M. J. Lehtinen. 2020. Gut microbiota, probiotics and physical performance in athletes and physically active individuals. *Nutrients* 12 (10).2936. doi: 10.3390/nu1210:.

Matthews, D. M., and L. Laster. 1965. Absorption of protein digestion products: A review. *Gut* 6 (5):411–26. doi: 10.1136/gut.6.5.411.

Meijnikman, A. S., V. E. Gerdes, M. Nieuwdorp, and H. Herrema. 2018. Evaluating causality of gut microbiota in obesity and diabetes in humans. *Endocrine Reviews* 39 (2):133–53. doi: 10.1210/er.2017-00192.

Mestre, L., F. J. Carrillo-Salinas, A. Feliú, M. Mecha, G. Alonso, C. Espejo, L. Calvo-Barreiro, J. L. Luque-García, H. Estevez, L. M. Villar, et al. 2020. How oral probiotics affect the severity of an experimental model of progressive multiple sclerosis? Bringing commensal bacteria into the neurodegenerative process. *Gut Microbes* 12 (1):1813532. doi: 10.1080/19490976.2020.1813532.

Mitchell, S. M., A. M. Milan, C. J. Mitchell, N. A. Gillies, R. F. D'souza, N. Zeng, F. Ramzan, P. Sharma, S. O. Knowles, N. C. Roy, et al. 2019. Protein intake at twice the rda in older men increases circulatory concentrations of the microbiome metabolite trimethylamine-n-oxide (tmao). *Nutrients* 11 (9):2207. doi: 10.3390/nu1109:2207.

Miyake, S., S. Kim, W. Suda, K. Oshima, M. Nakamura, T. Matsuoka, N. Chihara, A. Tomita, W. Sato, S.-W. Kim, et al. 2015. Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to clostridia xiva and iv clusters. *PLoS One* 10 (9):e0137429. doi: 10.1371/journal.pone.0137429.

Moreno-Pérez, D., C. Bressa, M. Bailén, S. Hamed-Bousdar, F. Naclerio, M. Carmona, M. Pérez, R. González-Soltero, M. G. Montalvo-Lominchar, C. Carabaña, et al. 2018. Effect of a protein supplement on the gut microbiota of endurance athletes: A randomized, controlled, double-blind pilot study. *Nutrients* 10 (3)337. doi: 10.3390/nu10030:.

Mötteli, S., C. Keller, M. Siegrist, J. Barbey, and T. Bucher. 2016. Consumers' practical understanding of healthy food choices: A fake food experiment. *The British Journal of Nutrition* 116 (3):559–66. doi: 10.1017/s0007114516002130.

Mozaffarian, D. 2016. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: A comprehensive review. *Circulation* 133 (2):187–225. doi: 10.1161/circulationaha.115.018585.

Obermeier, B., R. Daneman, and R. M. Ransohoff. 2013. Development, maintenance and disruption of the blood-brain barrier. *Nature Medicine* 19 (12):1584–96. doi: 10.1038/nm.3407.

Organization, W.H. WHO. 2007. Protein and amino acid requirements in human nutrition.

Pedersen, H. K., V. Gudmundsdottir, H. B. Nielsen, T. Hyotylainen, T. Nielsen, B. A. Jensen, K. Forslund, F. Hildebrand, E. Prifti, G. Falony, et al. 2016. Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature* 535 (7612):376–81. doi: 10.1038/nature18646.

Portune, K. J., M. Beaumont, A. M. Davila, D. Tomé, F. Blachier, and Y. Sanz. 2016. Gut microbiota role in dietary protein metabolism and health-related outcomes: The two sides of the coin. *Trends in Food Science & Technology* 57:213–32. doi: 0.1016/j.tifs.2016.08.011. doi: 10.1016/j.tifs.2016.08.011.

Portune, K. J., A. Benítez-Páez, E. M. Del Pulgar, V. Cerrudo, and Y. Sanz. 2017. Gut microbiota, diet, and obesity-related disorders-the good, the bad, and the future challenges. *Molecular Nutrition & Food Research* 61 (1):1600252. doi: 10.1002/mnfr.201600252.

Qin, J., R. Li, J. Raes, M. Arumugam, K. S. Burgdorf, C. Manichanh, T. Nielsen, N. Pons, F. Levenez, T. Yamada, et al. 2010. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 464 (7285):59–65. doi: 10.1038/nature08821.

Quigley, E. M. M. 2017. Microbiota-brain-gut axis and neurodegenerative diseases. *Current Neurology and Neuroscience Reports* 17 (12): 94. doi: 10.1007/s11910-017-0802-6.

Rampelli, S., M. Candela, S. Turroni, E. Biagi, S. Collino, C. Franceschi, P. W. O'toole, and P. Brigidi. 2013. Functional metagenomic profiling of intestinal microbiome in extreme ageing. *Aging* 5 (12):902–12. doi: 10.18632/aging.100623.

Rand, W. M., P. L. Pellett, and V. R. Young. 2003. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. *The American Journal of Clinical Nutrition* 77 (1): 109–27. doi: 10.1093/ajcn/77.1.109.

Rasmussen, L. G., H. Winning, F. Savorani, H. Toft, T. M. Larsen, L. O. Dragsted, A. Astrup, and S. B. Engelsen. 2012. Assessment of the effect of high or low protein diet on the human urine metabolome as measured by NMR. *Nutrients* 4 (2):112–31. doi: 10.3390/nu4020112.

Raybould, H. E. 2010. Gut chemosensing: Interactions between gut endocrine cells and visceral afferents. *Autonomic Neuroscience: Basic & Clinical* 153 (1-2):41–6. doi: 10.1016/j.autneu.2009.07.007.

Requena, T., M. C. Martínez-Cuesta, and C. Peláez. 2018. Diet and microbiota linked in health and disease. *Food & Function* 9 (2): 688–704. doi: 10.1039/c7fo01820g.

Research, Grand View. 2019. 2019–2025 (GVR, Protein ingredients market size, share & trends analysis report by product (plant, animal), by application (food & beverages, infant formulations, personal care & cosmetics), and segment forecasts.

Ridaura, V. K., J. J. Faith, F. E. Rey, J. Cheng, A. E. Duncan, A. L. Kau, N. W. Griffin, V. Lombard, B. Henrissat, J. R. Bain, et al. 2013. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science (New York, N.Y.)* 341 (6150):1241214. doi: 10.1126/science.1241214.

Rodríguez-Morató, J., N. R. Matthan, J. Liu, R. De La Torre, and C. Y. O. Chen. 2018. Cranberries attenuate animal-based diet-induced changes in microbiota composition and functionality: A randomized crossover controlled feeding trial. *The Journal of Nutritional Biochemistry* 62:76–86. doi: 10.1016/j.jnutbio.2018.08.019.

Russell, W. R., S. W. Gratz, S. H. Duncan, G. Holtrop, J. Ince, L. Scobbie, G. Duncan, A. M. Johnstone, G. E. Lobley, R. J. Wallace, et al. 2011. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. *The American Journal of Clinical Nutrition* 93 (5):1062–72. doi: 10.3945/ajcn.110.002188.

Salarkia, N., L. Ghadamli, F. Zaeri, and L. Sabaghian Rad. 2013. Effects of probiotic yogurt on performance, respiratory and digestive systems of young adult female endurance swimmers: A randomized controlled trial. *Medical Journal of the Islamic Republic of Iran* 27 (3):141–6.

Sale, C., and K. J. Elliott-Sale. 2019. Nutrition and athlete bone health. *Sports Medicine (Auckland, N.Z.)* 49 (Suppl 2):139–51. doi: 10.1007/s40279-019-01161-2.

Salehipour, Z., D. Haghmorad, M. Sankian, M. Rastin, R. Nosratabadi, M. M. Soltan Dallal, N. Tabasi, M. Khazaee, L. R. Nasiraii, and M. Mahmoudi. 2017. Bifidobacterium animalis in combination with human origin of lactobacillus plantarum ameliorate neuroinflammation in experimental model of multiple sclerosis by altering CD4+ t cell subset balance. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 95:1535–48. doi: 10.1016/j.biopha.2017.08.117.

Samal, J. R. K., and I. R. Samal. 2018. Protein supplements: Pros and cons. *Journal of Dietary Supplements* 15 (3):365–71. doi: 10.1080/19390211.2017.1353567.

Sanctuary, M. R., J. N. Kain, K. Angkustsiri, and J. B. German. 2018. Dietary considerations in autism spectrum disorders: The potential role of protein digestion and microbial putrefaction in the gut-brain axis. *Frontiers in Nutrition* 5:40. doi: 10.3389/fnut.2018.00040.

Santesso, N., E. A. Akl, M. Bianchi, A. Mente, R. Mustafa, D. Heels-Ansdell, and H. J. Schünemann. 2012. Effects of higher- versus lower-protein diets on health outcomes: A systematic review and meta-analysis. *European Journal of Clinical Nutrition* 66 (7):780–8. doi: 10.1038/ejcn.2012.37.

Schmedes, M., A. D. Brejnrod, E. K. Aadland, P. Kiilerich, K. Kristiansen, H. Jacques, C. Lavigne, I. E. Graff, Ø. Eng, A. Holthe, et al. 2019. The effect of lean-seafood and non-seafood diets on fecal metabolites and gut microbiome: Results from a randomized crossover intervention study. *Molecular Nutrition & Food Research* 63 (1):e1700976. doi: 10.1002/mnfr.201700976.

Schugar, R. C., D. M. Shih, M. Warrier, R. N. Helsley, A. Burrows, D. Ferguson, A. L. Brown, A. D. Gromovsky, M. Heine, A. Chatterjee, et al. 2017. The tmao-producing enzyme flavin-containing monooxygenase 3 regulates obesity and the beiging of white adipose tissue. *Cell Reports* 19 (12):2451–61. doi: 10.1016/j.celrep.2017.05.077.

Seo, D. B., H. W. Jeong, Y. J. Kim, S. Kim, J. Kim, J. H. Lee, K. Joo, J. K. Choi, S. S. Shin, and S. J. Lee. 2017. Fermented green tea extract exhibits hypolipidaemic effects through the inhibition of pancreatic lipase and promotion of energy expenditure. *The British Journal of Nutrition* 117 (2):177–86. doi: 10.1017/s0007114516004621.

Serena, C., V. Ceperuelo-Mallafré, N. Keiran, M. I. Queipo-Ortuño, R. Bernal, R. Gomez-Huelgas, M. Urpi-Sarda, M. Sabater, V. Pérez-Brocal, C. Andrés-Lacueva, et al. 2018. Elevated circulating levels of succinate in human obesity are linked to specific gut microbiota. *The ISME Journal* 12 (7):1642–57. doi: 10.1038/s41396-018-0068-2.

Sharon, G., N. J. Cruz, D. W. Kang, M. J. Gandal, B. Wang, Y. M. Kim, E. M. Zink, C. P. Casey, B. C. Taylor, C. J. Lane, et al. 2019. Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. *Cell* 177 (6):1600–18.e17. doi: 10.1016/j.cell.2019.05.004.

Siri-Tarino, P. W., Q. Sun, F. B. Hu, and R. M. Krauss. 2010. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *The American Journal of Clinical Nutrition* 91 (3):535–46. doi: 10.3945/ajcn.2009.27725.

Smith, J. D., T. Hou, D. S. Ludwig, E. B. Rimm, W. Willett, F. B. Hu, and D. Mozaffarian. 2015. Changes in intake of protein foods, carbohydrate amount and quality, and long-term weight change: Results from 3 prospective cohorts. *The American Journal of Clinical Nutrition* 101 (6):1216–24. doi: 10.3945/ajcn.114.100867.

So, D., K. Whelan, M. Rossi, M. Morrison, G. Holtmann, J. T. Kelly, E. R. Shanahan, H. M. Staudacher, and K. L. Campbell. 2018. Dietary fiber intervention on gut microbiota composition in healthy adults: A systematic review and meta-analysis. *The American Journal of Clinical Nutrition* 107 (6):965–83. doi: 10.1093/ajcn/nqy041.

Sonnenburg, J. L., and F. Bäckhed. 2016. Diet-microbiota interactions as moderators of human metabolism. *Nature* 535 (7610):56–64. doi: 10.1038/nature18846.

Spielman, L. J., D. L. Gibson, and A. Klegeris. 2018. Unhealthy gut, unhealthy brain: The role of the intestinal microbiota in neurodegenerative diseases. *Neurochemistry International* 120:149–63. doi: 10.1016/j.neuint.2018.08.005.

Stanislawski, M. A., D. Dabelea, L. A. Lange, B. D. Wagner, and C. A. Lozupone. 2019. Gut microbiota phenotypes of obesity. *NPJ Biofilms and Microbiomes* 5 (1):18. doi: 10.1038/s41522-019-0091-8.

Stock, M. J. 1999. Gluttony and thermogenesis revisited. *International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity* 23 (11):1105–17. doi: 10.1038/sj.ijo.0801108.

Sun, J., S. Liu, Z. Ling, F. Wang, Y. Ling, T. Gong, N. Fang, S. Ye, J. Si, and J. Liu. 2019. Fructooligosaccharides ameliorating cognitive deficits and neurodegeneration in app/ps1 transgenic mice through modulating gut microbiota. *Journal of Agricultural and Food Chemistry* 67 (10):3006–17. doi: 10.1021/acs.jafc.8b07313.

Tang, W. H. W., and S. L. Hazen. 2014. The contributory role of gut microbiota in cardiovascular disease. *The Journal of Clinical Investigation* 124 (10):4204–11. doi: 10.1172/JCI72331.

Tankou, S. K., K. Regev, B. C. Healy, L. M. Cox, E. Tjon, P. Kivisakk, I. P. Vanande, S. Cook, R. Gandhi, B. Glanz, et al. 2018. Investigation of probiotics in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 24 (1):58–63. doi: 10.1177/1352458517737390.

Tarr, A. J., J. D. Galley, S. E. Fisher, M. Chichlowski, B. M. Berg, and M. T. Bailey. 2015. The prebiotics 3'sialyllactose and 6'sialyllactose diminish stressor-induced anxiety-like behavior and colonic microbiota alterations: Evidence for effects on the gut-brain axis. *Brain, Behavior, and Immunity* 50:166–77. doi: 10.1016/j.bbi.2015.06.025.

Tayyem, R. F., H. A. Bawadi, I. Shehadah, L. M. Agraib, S. S. Abumweis, T. Al-Jaberi, M. Al-Nusairr, K. E. Bani-Hani, and D. D. Heath. 2017. Dietary patterns and colorectal cancer. *Clinical Nutrition* (*Edinburgh*, Scotland*)* 36 (3):848–52. doi: 10.1016/j.clnu.2016.04.029.

Ticinesi, A., F. Lauretani, C. Milani, A. Nouvenne, C. Tana, D. Del Rio, M. Maggio, M. Ventura, and T. Meschi. 2017. Aging gut microbiota at the cross-road between nutrition, physical frailty, and sarcopenia: Is there a gut-muscle axis. ? *Nutrients* 9 (12)1303. doi: 10.3390/nu912:.

Toden, S., A. R. Bird, D. L. Topping, and M. A. Conlon. 2007a. High red meat diets induce greater numbers of colonic DNA double-strand breaks than white meat in rats: Attenuation by high-amylose maize starch. *Carcinogenesis* 28 (11):2355–62. doi: 10.1093/carcin/bgm216.

Tong, X., J. Xu, F. Lian, X. Yu, Y. Zhao, L. Xu, M. Zhang, X. Zhao, J. Shen, S. Wu, et al. 2018. Structural alteration of gut microbiota during the amelioration of human type 2 diabetes with hyperlipidemia by metformin and a traditional Chinese herbal formula: A multicenter, randomized, open label clinical trial. *mBio* 9 (3):e02392–17. doi: 10.1128/mBio.02392-17.

Tremaroli, V., and F. Bäckhed. 2012. Functional interactions between the gut microbiota and host metabolism. *Nature* 489 (7415):242–9. doi: 10.1038/nature11552.

Turnbaugh, P. J., R. E. Ley, M. A. Mahowald, V. Magrini, E. R. Mardis, and J. I. Gordon. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444 (7122):1027–31. doi: 10.1038/nature05414.

Valcheva, R., P. Koleva, I. Martínez, J. Walter, M. G. Gänzle, and L. A. Dieleman. 2019. Inulin-type fructans improve active ulcerative colitis associated with microbiota changes and increased short-chain fatty acids levels. *Gut Microbes* 10 (3):334–57. doi: 10.1080/19490976.2018.1526583.

Vandeputte, D., G. Falony, S. Vieira-Silva, J. Wang, M. Sailer, S. Theis, K. Verbeke, and J. Raes. 2017. Prebiotic inulin-type fructans induce specific changes in the human gut microbiota. *Gut* 66 (11):1968–74. doi: 10.1136/gutjnl-2016-313271.

Verreijen, A. M., M. F. Engberink, R. G. Memelink, S. E. Van Der Plas, M. Visser, and P. J. M. Weijs. 2017. Effect of a high protein diet and/or resistance exercise on the preservation of fat free mass during weight loss in overweight and obese older adults: A randomized controlled trial. *Nutrition Journal* 16 (1):10. doi: 10.1186/s12937-017-0229-6.

Vulevic, J., A. Juric, G. Tzortzis, and G. R. Gibson. 2013. A mixture of trans-galactooligosaccharides reduces markers of metabolic syndrome and modulates the fecal microbiota and immune function of overweight adults. *The Journal of nutrition* 143 (3):324–31. doi: 10.3945/jn.112.166132.

Wagner, E. A., G. A. Falciglia, H. Amlal, L. Levin, and M. Soleimani. 2007. Short-term exposure to a high-protein diet differentially affects glomerular filtration rate but not acid-base balance in older compared to younger adults. *Journal of the American Dietetic Association* 107 (8):1404–8. doi: 10.1016/j.jada.2007.05.003.

Wang, H., X. Zhang, S. Wang, H. Li, Z. Lu, J. Shi, and Z. Xu. 2018. Mannan-oligosaccharide modulates the obesity and gut microbiota in high-fat diet-fed mice. *Food & Function* 9 (7):3916–29. doi: 10.1039/c8fo00209f.

Wang, Y., X. Cui, Q. Lin, J. Cai, L. Tang, and Y. Liang. 2020. Active peptide kf-8 from rice bran attenuates oxidative stress in a mouse model of aging induced by d-galactose. *Journal of Agricultural and Food Chemistry* 68 (44):12271–83. doi: 10.1021/acs.jafc.0c04358.

Wang, Z., E. Klipfell, B. J. Bennett, R. Koeth, B. S. Levison, B. Dugar, A. E. Feldstein, E. B. Britt, X. Fu, Y.-M. Chung, et al. 2011. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 472 (7341):57–63. doi: 10.1038/nature09922.

Welch, A. A. 2014. Nutritional influences on age-related skeletal muscle loss. *The Proceedings of the Nutrition Society* 73 (1):16–33. doi: 10.1017/s0029665113003698.

Wilson, B. 2019. Protein mania: The rich world's new diet obsession. *Guardian (Lond.).*

Windey, K., V. De Preter, and K. Verbeke. 2012. Relevance of protein fermentation to gut health. *Molecular Nutrition & Food Research* 56 (1):184–96. doi: 10.1002/mnfr.201100542.

Wosinska, L., P. D. Cotter, O. O'Sullivan, and C. Guinane. 2019. The potential impact of probiotics on the gut microbiome of athletes. *Nutrients* 11 (10):2270. doi: 10.3390/nu11102270.

Wright, C., J. Zhou, R. Sayer, J. Kim, and W. Campbell. 2018. Effects of a high-protein diet including whole eggs on muscle composition and indices of cardiometabolic health and systemic inflammation in older adults with overweight or obesity: A randomized controlled trial. *Nutrients* 10 (7):946. doi: 10.3390/nu10070946.

Wu, G. 2010. Functional amino acids in growth, reproduction, and health. *Advances in Nutrition (Bethesda, Md.)* 1 (1):31–7. doi: 10.3945/an.110.1008.

Wu, G. 2016. Dietary protein intake and human health. *Food & Function* 7 (3):1251–65. doi: 10.1039/c5fo01530h.

Wu, L., W. Yang, X. Jia, G. Yang, D. Duridanova, K. Cao, and R. Wang. 2009. Pancreatic islet overproduction of h2s and suppressed insulin release in zucker diabetic rats. *Laboratory Investigation* 89 (1):59–67. doi: 10.1038/labinvest.2008.109.

Wu, W.-K., C.-C. Chen, P.-Y. Liu, S. Panyod, B.-Y. Liao, P.-C. Chen, H.-L. Kao, H.-C. Kuo, C.-H. Kuo, T. H. T. Chiu, et al. 2019. Identification of tmao-producer phenotype and host-diet-gut dysbiosis by carnitine challenge test in human and germ-free mice. *Gut* 68 (8):1439–49. doi: 10.1136/gutjnl-2018-317155.

Yan, J., J. W. Herzog, K. Tsang, C. A. Brennan, M. A. Bower, W. S. Garrett, B. R. Sartor, A. O. Aliprantis, and J. F. Charles. 2016. Gut microbiota induce igf-1 and promote bone formation and growth. *Proceedings of the National Academy of Sciences of the United States of America* 113 (47):E7554–E63. doi: 10.1073/pnas.1607235113.

Yan, T., N. Wang, B. Liu, B. Wu, F. Xiao, B. He, and Y. Jia. 2021. Schisandra chinensis ameliorates depressive-like behaviors by regulating microbiota-gut-brain axis via its anti-inflammation activity. *Phytotherapy Research* 35 (1):289–96. doi: 10.1002/ptr.6799.

Yang, J., and J. Yu. 2018. The association of diet, gut microbiota and colorectal cancer: What we eat may imply what we get. *Protein & Cell* 9 (5):474–87. doi: 10.1007/s13238-018-0543-6.

Yang, Z., S. Huang, D. Zou, D. Dong, X. He, N. Liu, W. Liu, and L. Huang. 2016. Metabolic shifts and structural changes in the gut microbiota upon branched-chain amino acid supplementation in middle-aged mice. *Amino Acids* 48 (12):2731–45. doi: 10.1007/s00726-016-2308-y.

Zhang, L., G. Yang, A. Untereiner, Y. Ju, L. Wu, and R. Wang. 2013. Hydrogen sulfide impairs glucose utilization and increases gluconeogenesis in hepatocytes. *Endocrinology* 154 (1):114–26. doi: 10.1210/en.2012-1658.

Zhang, Y., G. Bobe, J. S. Revel, R. R. Rodrigues, T. J. Sharpton, M. L. Fantacone, K. Raslan, C. L. Miranda, M. B. Lowry, P. R. Blakemore, et al. 2020. Improvements in metabolic syndrome by xanthohumol derivatives are linked to altered gut microbiota and bile acid metabolism. *Molecular Nutrition & Food Research* 64 (1):e1900789. doi: 10.1002/mnfr.201900789.

Zhang, Z.,. J. E. Hyun, A. Thiesen, H. Park, N. Hotte, H. Watanabe, T. Higashiyama, and K. L. Madsen. 2020. Sex-specific differences in the gut microbiome in response to dietary fiber supplementation in il-10-deficient mice. *Nutrients* 12 (7):2088. doi: 10.3390/nu1207:2088.

Zhao, L., F. Zhang, X. Ding, G. Wu, Y. Y. Lam, X. Wang, H. Fu, X. Xue, C. Lu, J. Ma, et al. 2018. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science (New York, N.Y.)* 359 (6380):1151–6. doi: 10.1126/science.aao5774.

Zheng, J., H. Li, X. Zhang, M. Jiang, C. Luo, Z. Lu, Z. Xu, and J. Shi. 2018. Prebiotic mannan-oligosaccharides augment the hypoglycemic effects of metformin in correlation with modulating gut microbiota. *Journal of Agricultural and Food Chemistry* 66 (23):5821–31. doi: 10.1021/acs.jafc.8b00829.

Zhu, Y., E. Jameson, M. Crosatti, H. Schäfer, K. Rajakumar, T. D. H. Bugg, and Y. Chen. 2014. Carnitine metabolism to trimethylamine by an unusual rieske-type oxygenase from human microbiota. *Proceedings of the National Academy of Sciences of the United States of America* 111 (11):4268–73. doi: 10.1073/pnas.1316569111.

Zhu, Y., P. P. Wang, J. Zhao, R. Green, Z. Sun, B. Roebothan, J. Squires, S. Buehler, E. Dicks, J. Zhao, et al. 2014. Dietary n-nitroso compounds and risk of colorectal cancer: A case-control study in newfoundland and labrador and ontario, canada. *The British Journal of Nutrition* 111 (6):1109–17. doi: 10.1017/s0007114513003462.

Zimmer, J., B. Lange, J. S. Frick, H. Sauer, K. Zimmermann, A. Schwiertz, K. Rusch, S. Klosterhalfen, and P. Enck. 2012. A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. *European Journal of Clinical Nutrition* 66 (1):53–60. doi: 10.1038/ejcn.2011.141.

Zmora, N., J. Suez, and E. Elinav. 2019. You are what you eat: Diet, health and the gut microbiota. *Nature Reviews. Gastroenterology & Hepatology* 16 (1):35–56. doi: 10.1038/s41575-018-0061-2.