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Review

Rethinking healthy eating in light of the gut microbiome

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SUMMARY

Given the worldwide epidemic of diet-related chronic diseases, evidence-based dietary recommendations are fundamentally important for health promotion. Despite the importance of the human gut microbiota for the physiological effects of diet and chronic disease etiology, national dietary guidelines around the world are just beginning to capitalize on scientific breakthroughs in the microbiome field. In this review, we discuss contemporary nutritional recommendations from a microbiome science perspective, focusing on mechanistic evidence that established host-microbe interactions as mediators of the physiological effects of diet. We apply this knowledge to inform discussions of nutrition controversies, advance innovative dietary strategies, and propose an experimental framework that integrates the microbiome into nutrition research. The congruence of key paradigms in the nutrition and microbiome disciplines validates current recommendations in dietary guidelines, and the systematic incorporation of microbiome science into nutrition research has the potential to further improve and innovate healthy eating.

INTRODUCTION

Diet is central to human health and the etiology of noncommunicable chronic diseases that have reached epidemic proportions (Jaacks et al., 2019). A clear testament to the profound effects of diet on human health is the consistent escalation of chronic diseases in nonindustrialized populations that transition to a Western-style diet (Kopp, 2019). It is, therefore, crucial to identify what are health-promoting or detrimental foods and dietary patterns and to translate this evidence into dietary guidelines. Nutrition researchers combine observational studies, randomized controlled trials (RCTs), and mechanistic studies in animal models to achieve this (Williams et al., 2020). Systematic reviews and meta-analyses, which constitute the top of the evidence hierarchy, inform the development of national food-based dietary guidelines (Blake et al., 2018). Despite challenges in conducting nutritional studies (Hall, 2020), a range of rigorous prospective cohort studies and RCTs have provided robust validation for hallmarks of healthy eating: for example, the benefits of vegetables and fruit (Aune et al., 2017) and whole grains (Aune et al., 2016), and the detrimental effects of processed foods (Hall et al., 2019). However, many controversies still exist, resulting in widespread public confusion about what constitutes a healthy diet.

An important factor of the physiological effects of diet rarely considered in establishing dietary guidelines is the human gut microbiome. The gastrointestinal tract is colonized by a dense and complex assembly of microbes that contribute significantly to host metabolism and immunology (de Vos et al., 2022). Although the role of the gut microbiome in nutrition and health has been recognized for decades (Brown, 1977), the emergence and increased affordability of sequencing and multi-omics technologies have spurred a convergence of the microbiome and nutrition disciplines into one of the most promising areas in the health sciences (Shanahan and Murphy, 2011). The two fields share commonalities in relation to diseases and physiological states studied and experimental approaches used (Shanahan et al., 2021). Virtually all diet-related chronic diseases have also been linked to the microbiome (Sekirov et al., 2010), supporting its role as a mediator by which diet influences disease risk. Although microbiome science, analogous to the nutrition field, has suffered from overreliance on correlative studies (Fischbach, 2018), which cannot assign causality in humans (Walter et al., 2020), diet-induced pathological phenotypes in animal models are often microbiome dependent, and mechanisms by which the microbiome influences pathophysiology have been identified (Bäckhed et al., 2007; Lindskog Jonsson et al., 2018). These discoveries provide a strong scientific rationale to incorporate the gut microbiome in nutrition research and dietary guidelines. Accordingly, the American Society for Nutrition recently established the "Nutritional Microbiology" research interest section to investigate interactions between dietary compounds and gut microbiota, focusing on basic and translational research (American Society for Nutrition, 2021).

Although research at the interface of the nutrition and microbiome disciplines has increased recently, there has been limited consideration of diet-microbiome-host interactions in contemporary dietary recommendations. Here, we discuss national

food-based dietary guidelines and aspects of healthy eating in light of the gut microbiome. We limit our discussions to recommendations for health promotion and disease prevention in the general population, which is the purpose of food-based dietary guidelines (Blake et al., 2018). We focus on research demonstrating mechanistic insight into how the gut microbiome influences and mediates physiological effects of dietary compounds, specific foods, and dietary patterns. We then apply this evidence to inform ongoing controversies in the nutrition field, propose microbiome-targeted nutritional strategies, and outline an experimental framework for systematic incorporation of the gut microbiome into future nutrition research.

DIETARY GUIDELINES FROM AROUND THE WORLD ARE HIGHLY CONSISTENT

Food-based dietary guidelines provide recommendations on foods, food groups, and dietary patterns to achieve reference intakes of nutrients, prevent chronic diseases, and maintain overall health in the general population (FAO, 2022). Table 1 shows a non-exhaustive overview of key messages from national food-based dietary guidelines updated in the last 10 years, organized into the most common and complementary food groups: vegetables and fruits, grain products, dairy products, meat and meat alternatives (Herforth et al., 2019), and processed foods. Although these guidelines originate from different countries with diverse dietary cultures, there are strong consistencies, e.g., more than half of diet should constitute vegetables, fruits, and grain products, with whole grains prioritized over refined grains. These foods are to be complemented by smaller portions of animal-based (fish, lean meats, poultry, eggs, and dairy products) and/or plant-based proteins (legumes, nuts). Foods high in added sugar, salt, and saturated fat are recommended by all guidelines to be limited or avoided, with some countries specifically referring to the avoidance of processed, ultra-processed, and/or packaged foods. These national food-based dietary guidelines agree with other influential platforms of dietary recommendations, such as the Healthy Eating Plate of the Harvard T.H. Chan School of Public Health (Harvard University, 2011) and the *EAT*-Lancet Commission on healthy diets and sustainable food systems (Willett et al., 2019).

INTERACTIONS BETWEEN RECOMMENDED FOODS AND GUT MICROBIOTA

With few exceptions, such as the 2013 Food-Based Dietary Guidelines for South Africa (Vorster et al., 2013) and the 2020–2025 Dietary Guidelines for Americans (Dietary Guidelines Advisory Committee, 2020), dietary guidelines do not mention the gut microbiome. Below, we discuss dietary guidelines in the context of the microbiome, focusing on human studies and, despite their limitations (e.g., megadosing and translation to humans), animal models due to their strength in establishing molecular mechanisms and cause-and-effect relationships (Round and Palm, 2018).

Whole-plant foods versus processed foods

In all dietary guidelines, whole-plant foods such as vegetables, fruits, whole grains, legumes, and nuts are recommended at the expense of processed foods containing added sugar, salt, or saturated fats (Table 1). Whole-plant foods are the sole relevant, naturally occurring source of dietary fibers, which are indigestible carbohydrate polymers differing vastly in chemical composition, physicochemical properties, and physiological effects (Deehan et al., 2017). Of particular relevance to the gut microbiome are fermentable fibers, also referred to as microbiota-accessible carbohydrates (MACs) (Sonnenburg and Sonnenburg, 2014) and, if they show established health benefits linked to selective effects on the microbiome, prebiotics (Gibson et al., 2017). Fiber provides growth substrates for microbes that inhibit mucus-glycan metabolism, preventing gut-mucus depletion, encroachment of bacteria into the mucus layer, and downstream inflammation (Earle et al., 2015) and infections (Desai et al., 2016) in mice. The primary end-products of fiber fermentation are short-chain fatty acids (SCFAs), namely acetate, propionate, and butyrate, which evoke a wide variety of physiological effects (Blaak et al., 2020). These range from ecological effects on the microbial community (e.g., antimicrobial properties, reduced oxygen diffusion into the intestinal lumen), effects on gut barrier function (e.g., induction of tight-junction proteins, mucus production), and direct metabolic and immunological effects on the host (e.g., enhanced production of hormones that control satiety, increased adipose tissue lipolysis, and improved insulin sensitivity) (Blaak et al., 2020).

Another key component of whole-plant foods are phytochemicals, which are nonnutritive and bioactive compounds typically bound to dietary fibers that give plants their color, flavor, smell, and astringency (Valdés et al., 2015). The majority (90%–95%) of phytochemicals are not absorbed in the small intestine and, thus, partake in bidirectional interactions with gut microbiota. Gut microbes are responsible for biotransformation of phytochemicals via processes such as demethylation, ring cleavage, and dehydroxylation (Singh et al., 2020), which can increase their bioavailability, absorption, and antioxidative and immunomodulatory effects (Chang et al., 2019).

Despite beneficial effects of whole-plant foods, their consumption in industrialized countries is consistently lower than what is recommended at the expense of packaged foods that have undergone various degrees of processing (Marino et al., 2021). According to the NOVA food classification tool, the extent of food processing is the main driver of diet quality, and foods with the highest degree of processing are categorized as ''ultra-processed foods'' (Monteiro et al., 2019). Brazilian dietary guidelines recommend avoiding such foods (Table 1), and their detrimental effects (increased energy intake and weight gain) have been experimentally validated in a rigorously controlled-feeding study (Hall et al., 2019). However, there is little consistency in the definition of ultra-processed foods or examples of foods in this category, and controversy exists regarding blanket recommendations to avoid all ultra-processed foods without considering their individual nutritional attributes (Gibney, 2019). Nevertheless, the functional characteristics of processed foods are fundamentally different from whole-plant foods. Processed foods often have a higher energy density (Hall et al., 2019) and lack the three-dimensional structures present in plant cells (Augustin et al., 2020). As a consequence, nutrients are primarily acellular (i.e., not contained within cells) and are more readily available to host digestion (Spreadbury, 2012), which increases

Table 1. Non-exhaustive list of national food-based dietary guidelines and recommended intakes of food groups for the general adult population[a,b].

Country, Year Updated, *Official Name*	Vegetables and Fruits	Grain Products	Dairy Products	Meat and Meat Alternatives	Processed Foods
Saudi Arabia, 2012, الدليل الغذائي الصحي	Consume 3–5 servings of vegetables daily. Consume 2–4 servings of fruits daily. Make second largest component of diet.	Consume 6–11 servings of cereals and bread daily; choose those prepared from whole grains or cereals. Make largest component of diet.	Consume 2–4 servings of low–fat milk and dairy products daily. Make third largest component of diet (joint with meats and legumes group).	Consume 2–3 servings of lean meat and meat alternatives daily. Make third largest component of diet (joint with milk and dairy products group).	Limit intake of foods of poor nutritional value like food enriched with salt, sugars, saturated fats, and hydrogenated fat.
South Africa, 2013, *Food-Based Dietary Guidelines for South Africa*	Consume plenty and a variety of vegetables and fruit daily.	Consume unrefined and whole grain starchy foods with most meals. These guidelines discuss benefits of consuming different non-digestible carbohydrates due to fermentation by gut microbes.	Consume milk, maas (popular regional fermented milk), or yogurt daily.	Consume dry beans, split peas, lentils and soya regularly. Consume 2–3 servings of fish and ~4 eggs weekly. Limit lean meat to ≤90 g daily.	Limit intake of foods high in sugar and salt.
Brazil, 2014, *Guia Alimentar para a População Brasileira*	Grouped under "natural or minimally-processed foods"; make this food group basis of diet.	Grouped under "natural or minimally-processed foods"; make this food group basis of diet. Limit breads (classified as "processed foods").	Grouped under "natural or minimally-processed foods"; make this food group basis of diet. Limit cheeses (classified as "processed foods"), and milk drinks and yogurts that are sweetened, colored, or flavored (considered "ultra-processed foods").	Grouped under "natural or minimally-processed foods"; make this food group basis of diet. Emphasizes consuming foods of plant origin with small quantities of foods of animal origin.	Ultra-processed foods should be avoided (including processed meats).
Colombia, 2015, *Guías Alimentarias Basadas en Alimentos para la población colombiana mayor de 2 años*	Eat at least 5 servings of fruits and vegetables daily. Make ~¼ of diet.	Grains, root vegetables, tubers, and plantains are included in this group. Make ~¼ of diet.	Consume milk and dairy daily; at least 2 glasses of milk or dairy products daily. Make ~¼ of diet.	Meat, eggs, and dried legumes are included in this group. Eat legumes at least twice weekly and an egg once daily. Make ~$^1/_5$ of diet.	Reduce consumption of "packaged products" (including processed meats and foods high in salt and sugars).
Mexico, 2015, *Guías Alimentarias y de Actividad Física en contexto de sobrepeso y obesidad en la población mexicana*	Consume 3 or more servings of vegetables daily. Eat whole fruits (with peel), 2–3 servings daily. Make ~$^1/_3$ of diet.	Consume cereals daily (and combine with legumes). Aim for half of the servings to be whole grains. Make ~$^1/_3$ of diet.	Make ~$^1/_3$ of diet (together with other foods of animal origin and legumes).	Eat legumes daily (and combine with whole grains), and more often than foods of animal origin. Consume lean meats such as chicken or turkey. Make ~$^1/_3$ of diet (together with dairy products).	Reduce consumption of processed or packaged foods high in fat, sugar, and salt.

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Table 1. ***Continued***

Country, Year Updated, *Official Name*	Vegetables and Fruits	Grain Products	Dairy Products	Meat and Meat Alternatives	Processed Foods
Sweden, 2015, *Hitta ditt sätt att äta grönare, lagom mycket och röra på dig*	Consume 500 g of a variety of vegetables and fruits daily.	Consume whole grain products of pasta, bread, grains, and rice; 70 g of whole grains for women and 90 g for men.	Consume low-fat and unsweetened dairy products daily.	Consume 2 tablespoons of nuts and seeds daily. Consume fish and shellfish 2–3 times weekly. Consume ≤500 g of meat weekly.	Limit high-salt and high-sugar foods (including processed meats).
Argentina, 2016, *Guías alimentarias para la población Argentina*	Consume 5 portions of vegetables and fruits, varied in color and type, daily. Make largest component of diet.	Cereals, breads, potatoes, and legumes are included in this food group. Make second largest component of diet.	Consume low-fat milk, yogurt, and cheese 3 times daily. Make third largest component of diet.	Meat, eggs, and fish included in this food group; emphasizes consuming fish and eggs. Consume fish 3 times weekly. Make fourth largest component of diet.	Limit consumption of foods high in fat, sugar, and salt (including processed meats).
China, 2016, *中国居民膳食指南*	Consume 300–500 g of vegetables daily, with half being dark green. Consume 200–350 g of fruits daily. Make second largest component of diet.	Consume 250–400 g of cereal and potatoes daily, including 50–150 g of whole grains. Make largest component of diet.	Consume 300 g of milk and dairy products daily. Soybeans and nuts are included in this food group. Consume 25–35 g soybeans and nuts daily. Make fourth largest component of diet.	Consume 120–200 g of fish, poultry, eggs, and lean meat daily. Make third largest component of diet.	Reduce intake of salt, oil, and sugar. Limit smoked and cured meat consumption.
Ireland, 2016, *Healthy Food for Life – the Healthy Eating Guidelines*	Consume 5–7 servings of vegetables, salad, and fruits daily. Make largest component of diet.	Consume 3–5 servings of wholemeal cereals and breads, potatoes, pasta, and rice daily. Make second largest component of diet.	Consume 3 servings of low-fat milk, yogurt, and cheese daily. Make third largest component of diet.	Consume 2 servings of lean meat, poultry, fish, eggs, beans, and nuts daily. Make fourth largest component of diet.	Limit high-fat, salt, and sugar foods to maximum 1–2 times weekly. Limit processed salty meats.
United Kingdom, 2016, *Eatwell Guide*	Consume at least 5 servings of a variety of vegetables and fruits daily. Make largest component of diet (joint with grain products).	Choose whole grain or higher fiber breads, pasta, rice, potatoes, and other starchy carbohydrates. Make largest component of diet (joint with vegetables and fruits).	Consume low-fat and lower sugar milk and dairy foods or dairy alternatives. Make fourth largest component of diet.	Consume legumes, fish, eggs, meat, and other proteins (promotes legumes as meat alternatives). Consume 2 servings of fish weekly. Make third largest component of diet.	Limit foods high in fat, salt, and sugars. Eat less processed meat.
Germany, 2017, *Vollwertig essen und trinken nach den 10 Regeln der Deutsche Gesellschaft für Ernährung*	Consume at least 3 servings of vegetables and 2 servings of fruits daily. Make largest component of diet.	Choose whole grain varieties of breads, noodles, rice, and flours. Make second largest component of diet.	Consume milk and dairy products daily. Make third largest component of diet.	Consume fish 1–2 times weekly. Consume ≤300–600 g of meat weekly. Make fourth largest component of diet.	Avoid processed foods ("*verarbeitete Lebensmittel*") as they are high in fat, sugar, and salt.

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Table 1. ***Continued***

Country, Year Updated, *Official Name*	Vegetables and Fruits	Grain Products	Dairy Products	Meat and Meat Alternatives	Processed Foods
Kenya, 2017, *National Guidelines for Healthy Diets and Physical Activity*	Consume 5 servings of green leafy, red, and yellow vegetables and fruits daily; include a variety of other vegetables and fruit.	Consume whole or unprocessed starchy foods as part of meals daily.	Consume fresh milk, fermented milk, and yogurt daily. Use low-fat or skim milk.	Consume peas, lentils, cowpeas, pigeon peas, soya, nuts, and edible seeds at least 4 times weekly. Consume lean meat, fish and seafood, poultry, insects, or eggs at least twice weekly.	Avoid processed foods containing trans fatty acids, as well as sugar-rich, salty, and high-fat foods.
Pakistan, 2018, *Pakistan Dietary Guidelines for Better Nutrition*	Consume 5 servings of vegetables and fruits daily. Make largest component of diet.	Consume 6 ounces cereals daily; at least half being whole grains. Make second largest component of diet.	Consume 2–3 servings of milk and milk products daily. Make fourth largest component of diet.	Consume 2–3 servings of meat and legumes daily. Legumes are encouraged. Consume meat, fish, and eggs in moderation. Make third largest component of diet.	Limit intake of fatty foods and highly processed foods.
Canada, 2019, *Canada's Food Guide*	Consume a variety of vegetables and fruits regularly. Make ~½ of diet.	Consume whole grain foods regularly. Make ~¼ of diet.	Low-fat milk and dairy products and fortified soy beverages included in 'protein foods' group (make ~¼ of diet).	Legumes, nuts, seeds, lean meats and poultry, fish, shellfish, and eggs included in 'protein foods' group (make ~¼ of diet). Consume protein foods that come from plants more often.	Limit highly-processed foods high in sodium, free sugars, and saturated fat (including processed meats).
France, 2019, *Recommandations Alimentaires du Programme National Nutrition Santé*	Consume 5 servings of vegetables and fruits daily.	Consume the whole grain version when starches are grain-based; consume at least one whole grain starch daily.	Consume 2 servings of dairy products daily.	Consume pulses at least twice weekly or as an alternative to meat and poultry. Consume a small handful of nuts daily. Consume fish twice weekly. Favour poultry, and limit red meats to ≤500 g weekly.	Limit sugary, fatty, and salty foods. Limit processed meat to 150 g weekly.
New Zealand, 2020, *Eating and Activity Guidelines for New Zealand Adults*	Consume 5–6 servings of vegetables and 2 servings of fruits daily. Make largest component of diet.	Consume 6 servings of grain foods daily, mostly whole grain and naturally high in fiber. Make second largest component of diet.	Consume 2 ½ servings of low-fat milk and milk products daily. Make fourth largest component of diet.	Consume 2 ½–3 servings of legumes, seeds, fish, seafood, eggs, poultry, and/or lean red meats daily. Make third largest component of diet.	Limit intake of highly processed foods that are high in refined grains, saturated fat, salt, and sugar and low in nutrients (including processed meats).
United States of America, 2020, *Dietary Guidelines for Americans*	Consume 2 ½ cups of vegetables daily (emphasis on dark green, red, and orange types). Beans, peas, and lentils also included in this group. Consume 2 cups of fruits daily; at least half being whole fruits (not juices).	Consume 6 ounces of grains daily; at least half being whole grains. Refined-grain choices should be enriched.	Consume 3 cups of low-fat dairy and fortified soy alternatives daily. Most choices should be fat-free or low-fat.	Consume 5 ½ ounces daily of protein foods, including meats, poultry, eggs, seafood, nuts, seeds, beans, peas, lentils, and soy products. Meats and poultry should be lean or low-fat.	Limit foods high in added sugars, saturated fat, and sodium (including processed meats).

[a]Includes countries that have updated their dietary guidelines in the last 10 years (i.e., 2012 or later). Information on dietary guidelines, including their official names, were obtained from: http://www.fao.org/nutrition/education/food-based-dietary-guidelines.

[b]Virtually all guidelines also emphasize drinking low- or no-calorie beverages, such as water and tea, as main contributors to fluid intake and to avoid sugar-sweetened beverages.

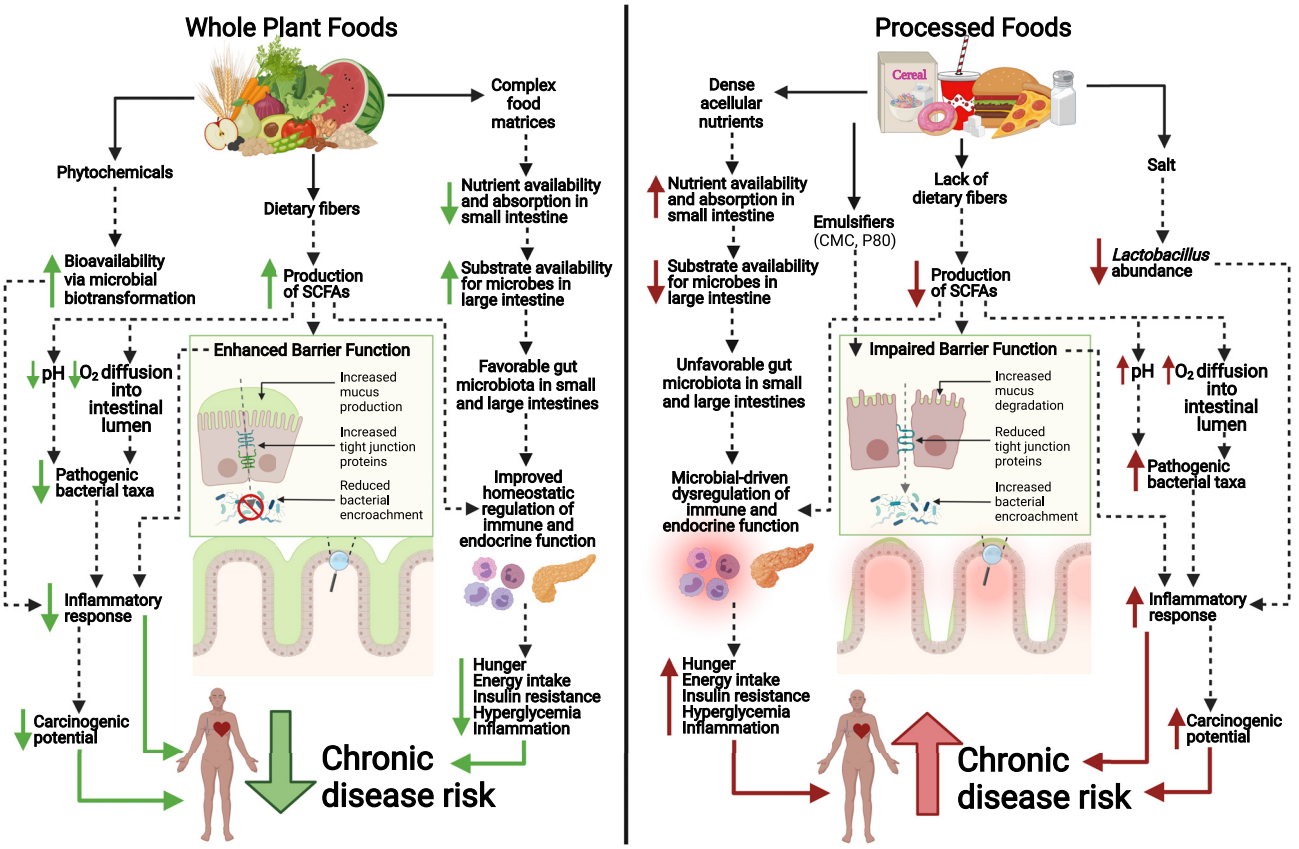

Figure 1. Comparison of the effects of whole-plant foods and processed foods on the gut microbiome and implications for host physiology, immunology, metabolism, and disease risk

Whole-plant foods provide phytochemicals and dietary fibers that, via their biotransformation by gut microbiota, are health-promoting through numerous mechanisms. In contrast, processed foods elicit negative effects on the gut environment due to the absence of these compounds and the presence of emulsifiers, salt, and acellular nutrients. CMC, carboxymethylcellulose; P80, polysorbate 80; SCFA, short-chain fatty acid.

nutrient-absorption kinetics (Juul et al., 2021). These easily fermentable nutrients may promote bacterial overgrowth in the small intestine and an unfavorable microbial compositional and metabolic profile, which negatively influence immune and endocrine functions (Zinöcker and Lindseth, 2018), while they are not available to colonic microbiota (Spreadbury, 2012). For example, high-fructose corn syrup has been shown to cause fatty liver and glucose intolerance in mice in a way linked to gut microbiota compositional and functional changes (Bhat et al., 2021).

Processed foods can further contain food additives to enhance mouthfeel and shelf-life that affect gut microbiota. The synthetic emulsifiers carboxymethylcellulose (CMC) and polysorbate-80 impaired gut barrier function and led to microbiota epithelial encroachment, promoting metabolic abnormalities and low-grade inflammation in wild-type mice and colitis in genetically susceptible mice, in a way causally linked to the gut microbiome (Chassaing et al., 2015). Similar findings were observed in mice for another emulsifier, glycerol monolaurate (Jiang et al., 2018). Short-term consumption of CMC in humans also significantly altered microbiota composition, reducing fecal SCFA levels, and inducing bacterial encroachment into the mucus layer (Chassaing et al., 2022). The high salt content in processed foods might also alter the microbiome. Salt consumption decreased *Lactobacillus* abundance, which was linked to increased T helper 17 cell numbers in murine small intestinal lamina propria lymphocytes and human peripheral blood lymphocytes, as well as higher blood pressure (Wilck et al., 2017). Another study in mice reported similar results, where a high-salt diet reduced *Lactobacillus* abundance, increased proinflammatory gene expression, and exacerbated colitis in two separate disease models (Miranda et al., 2018). Thus, the available evidence suggests that the contrasting effects of processed and whole-plant foods on human health are, in part, mediated by the gut microbiome (Figure 1).

Vegetables and fruits

According to dietary guidelines, the largest component of a healthy diet should be vegetables and fruits (Table 1). The scientific evidence for their ability to prevent numerous chronic diseases is strong (Aune et al., 2017). Fruits and vegetables provide up to 8 g of dietary fiber per serving (Dahl and Stewart, 2015) and contain a high diversity of fibers, including pectins, inulin, cellulose, xyloglucans, raffinose, and stachyose (Cui et al., 2019; Jovanovic-Malinovska et al., 2014). These fibers elicit both microbiome-independent (e.g., delayed macronutrient absorption)

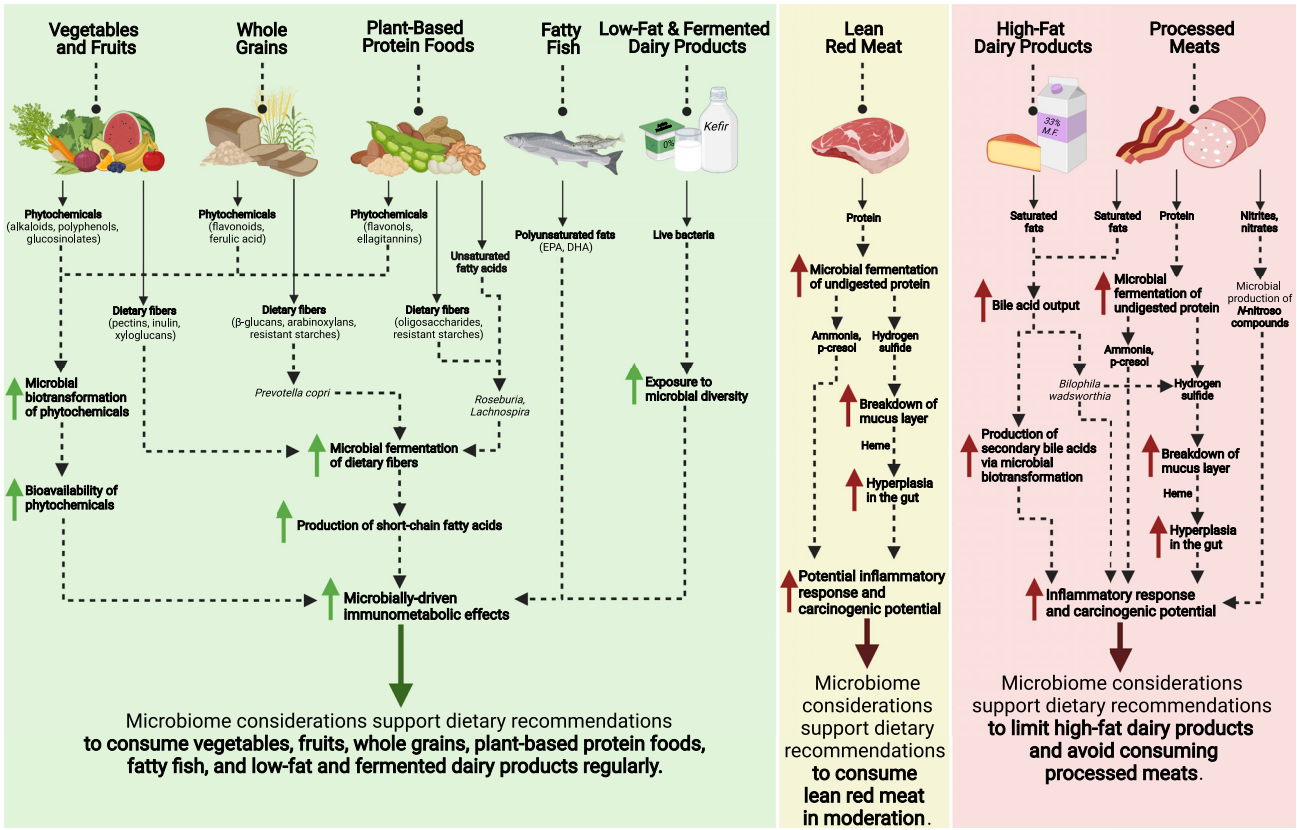

Figure 2. Effects of foods and food groups on host-microbe interactions and how they align with recommendations in dietary guidelines
Vegetables, fruits, whole grains, plant-based protein foods, fatty fish, and low-fat and fermented dairy products are consistently recommended in dietary guidelines to be consumed regularly (green box); these products provide various dietary components (fiber, phytochemicals, unsaturated fatty acids, and live bacteria) that benefit health via their interactions with gut microbiota. In contrast, most guidelines suggest moderate consumption of lean red meat (yellow box), which elevates several potentially detrimental microbial metabolites in the gut (ammonia, p-cresol, hydrogen sulfide). High-fat dairy products and processed meats are proposed to be avoided in dietary guidelines (red box). These foods are rich in saturated fats that have detrimental effects on host health via increases in secondary bile acids and abundance of pathobionts (e.g., *Bilophila wadsworthia*). Additionally, processed meats and some cheeses include nitrates and nitrites that are metabolized via microbial biotransformation into genotoxic compounds. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

and microbiome-dependent (e.g., SCFA-mediated attenuation of insulin resistance) physiological effects (Cui et al., 2019).

Controlled-feeding trials in humans have reported that vegetables rich in inulin increased *Bifidobacterium* levels, promoted satiety, and reduced body weight (Hiel et al., 2019, 2020). In mice fed a high-fat diet, antibiotic treatment reduced the metabolic benefits of inulin, such as induction of the incretin hormone glucagon-like peptide 1 in the small intestine and protection from metabolic syndrome, suggesting a causal role of the microbiota (Zou et al., 2018). Vegetables and fruits are also important sources of phytochemicals, including polyphenols, glucosinolates, terpenoids, phytosterols, and alkaloids (Somani et al., 2015). Cranberry extract, a rich source of polyphenols, induced improvements in metabolism (e.g., reduced visceral obesity and improved insulin sensitivity) in mice on a high-fat high-sucrose diet that were associated with an increase in *Akkermansia muciniphila* (Anhê et al., 2015), a bacterium that has shown beneficial physiological effects in both animals (Cani and de Vos, 2017) and humans (Depommier et al., 2019). There is also emerging evidence for a role of the microbiome in the physiological effects of broccoli from clinical (Kaczmarek et al., 2019) and preclinical studies. The latter established a genetic and biochemical basis in *Bacteroides thetaiotaomicron* for the bioactivation of broccoli-derived glucosinolates into chemopreventative isothiocyanates (Liou et al., 2020). Overall, available evidence supports a role of the gut microbiome in mediating well-established health effects of vegetables and fruits (Figure 2).

Whole grains

Most dietary guidelines recommend consuming whole grains over refined grains (Table 1). The bran layer of whole grains, which is removed to produce refined grains, contains phytochemicals (e.g., ferulic acid, flavonoids) and dietary fiber (Călinoiu and Vodnar, 2018). Whole grains contain unique hemicellulose fibers, such as xylans and β-(1 → 3,1 → 4)-glucans, in addition to cellulose, resistant starches, and oligosaccharides (Zhang and Hamaker, 2010). The evidence base for the ability of whole grains to reduce the risk of chronic diseases is convincing (Aune et al., 2016), and the potential role of gut microbiota in these effects has been increasingly investigated. Human intervention trials have shown anti-inflammatory effects of whole grains occurring in parallel to changes in gut microbiota. In healthy adults, Martínez et al. (2013) showed an enrichment of putative health-promoting organisms, such as *Bifidobacterium*

and butyrate producers (*Eubacterium rectale*, *Roseburia faecis*, and *Roseburia intestinalis*), while Venegas et al. (2017) showed enhancement of the SCFA producer *Lachnospira*, increased fecal acetate and total SCFAs, and reduced *Enterobacteriaceae*. Although microbiome changes provide potential explanations for anti-inflammatory effects, they were not consistent between these studies; further studies reported no effect (Roager et al., 2019), and causality was not established.

Elegant research combining a human study with mechanistic experiments in mice suggests a causal contribution of the microbiome in the health effects of whole grains. Humans who consumed barley kernel-based bread were grouped into "responders," whose glucose metabolism improved due to the intervention, and "nonresponders." High *Prevotella*/*Bacteroides* ratios and *Prevotella copri* abundance and microbial genes encoding for complex polysaccharide degradation were elevated in responders (Kovatcheva-Datchary et al., 2015). Germ-free mice gavaged either with *Prevotella copri* or "responder" human-derived microbiomes containing *P. copri* showed improvements in glucose tolerance when fed standard chow diets, which was mechanistically associated with increased hepatic glycogen storage (Kovatcheva-Datchary et al., 2015). Further research has confirmed that harboring high levels of *Prevotella* at baseline resulted in increased weight loss in individuals with excess body weight who consumed whole grain-rich diets (Roager and Christensen, 2022). These studies suggest that at least some of the metabolic benefits of whole grains are mediated by the gut microbiome (Figure 2).

Plant-based protein foods

Several dietary guidelines (Canada's Food Guide, Dietary Guidelines for the Brazilian Population, and the United Kingdom's Eatwell Guide) recommend that plant-based protein foods (e.g., legumes, nuts) should be consumed often due to their benefits to human and planetary health (Table 1). Legumes are rich in fiber, specifically cellulose, pectins, mannans, stachyose, raffinose, and resistant starches (Brummer et al., 2015). Legumes also contain phytochemicals such as flavonols, a subgroup of flavonoids known to be anti-inflammatory, and phenolic acids, which can be more bioavailable compared with those in grains (Awika et al., 2018). Emerging evidence suggests a role for the gut microbiome in the health effects of legumes (Figure 2). For example, mung-bean supplementation reduced weight gain and fat accumulation in mice fed high-fat diets but not in germ-free mice fed the same diets (Nakatani et al., 2018).

Nuts are sources of unsaturated fatty acids, fiber, and phytochemicals, all of which may influence host-microbe interactions. Daily supplementation of walnuts in a controlled-feeding study increased relative abundances of *Faecalibacterium*, *Roseburia*, *Clostridium*, and *Dialister* (Holscher et al., 2018a). Similar compositional changes were observed in a controlled-feeding study with almonds, showing increased relative abundances of *Roseburia*, *Clostridium*, *Dialister*, and *Lachnospira* (Holscher et al., 2018b). The effects of nut consumption on *Roseburia* levels have also been confirmed in a meta-analysis (Creedon et al., 2020). These bacteria produce butyrate, with *Roseburia intestinalis* specifically able to metabolize the indigestible glycans β-mannans found in nuts into butyrate (La Rosa et al., 2019). *Roseburia* may also be enhanced by omega-3 fatty acids in nuts, as its relative abundance was increased in humans as a result of both a walnut-supplemented diet and a diet with the same fatty-acid composition without walnuts (Tindall et al., 2020). In addition to fibers and unsaturated fatty acids in nuts, gut microbes metabolize the phytochemicals ellagitannins and ellagic acid into urolithins, which are bioactive anti-inflammatory compounds (Kim et al., 2017). Altogether, increased nut consumption appears to benefit host health in part via functional components impacting the microbiome (Figure 2).

Despite promising findings linking benefits of plant-based protein foods with the microbiome, research in this area is preliminary. Plant-based proteins are less digestible than animal-based proteins (Deane et al., 2020) and therefore provide potential substrates to colonic microbes, which may result in the production of beneficial bioactive metabolites, e.g., from tryptophan metabolism (Gao et al., 2018). However, proteolytic microbial fermentation is also potentially detrimental (see discussion below—red and processed meats). At present, it is unknown whether the metabolic outcomes from microbial fermentation of plant-based proteins differs from animal-based proteins, and future research in this area is needed.

Fish

Fish is consistently encouraged in dietary guidelines as a high-quality protein source and for its favorable fatty-acid profile (Table 1). Fatty fish is one of the main naturally occurring dietary sources of long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Vannice and Rasmussen, 2014). Strong evidence from observational (Jiang et al., 2021) and intervention studies (Alhassan et al., 2017) suggest a cardioprotective effect of increased fatty fish intake, and the gut microbiome could be a potential mediator of these health effects.

Experiments in mice demonstrated that, compared with lard (rich in saturated fats), fish oil lowered Toll-like receptor activation and white adipose tissue inflammation, which has been linked to improved insulin sensitivity (Caesar et al., 2015). In addition to distinct effects of the two fats on microbiota composition (i.e., lard enhanced *Bilophila*), both germ-free and antibiotic-treated mice colonized with cecal microbiomes from mice fed fish oil gained less weight and had reduced white adipose tissue inflammation compared with conventionally raised mice fed lard (Caesar et al., 2015). This study provides evidence for the causal role of gut microbiota in the inflammatory effects of saturated fats, which was mitigated with fish oil.

Causal inferences have not been made in humans, but omega-3 fatty acids found in fatty fish and other dietary sources have been proposed as candidate prebiotics as they are utilized by specific gut microbes (Gibson et al., 2017). In an RCT, a fish-derived omega-3 supplement increased *Coprococcus* spp. abundance that negatively correlated with triglyceride-rich lipoprotein levels (Vijay et al., 2021). Therefore, the gut microbiome is a probable mediator in the cardioprotective effects of polyunsaturated fatty acids (Figure 2).

FOCUS ON DIETARY PATTERNS: THE MEDITERRANEAN DIET

The realization that health is not primarily influenced by individual foods but by their interconnectedness and synergistic effects led

to a shift in focus on dietary patterns in several recently updated dietary guidelines, such as the 2020–2025 Dietary Guidelines for Americans (Dietary Guidelines Advisory Committee, 2020) and Canada's Food Guide (Health Canada, 2019). Interactions among foods are also relevant for their effects on the gut microbiome, and there has been significant interest in how dietary patterns, especially those with established health benefits such as the Mediterranean diet, influence host health via microbiome compositional and functional changes (Tindall et al., 2018). By recommending vegetables, fruits, whole grains, legumes, nuts, and olive oil as dietary staples, moderate intake of fish, poultry, eggs, and dairy products, and limiting intake of red and processed meats and processed foods (Davis et al., 2015), the Mediterranean diet combines many of the food groups discussed above that have favorable effects on host-microbe interactions.

In an RCT conducted in individuals with excess body weight, increased adherence to a Mediterranean diet decreased plasma cholesterol concentrations and enriched *Faecalibacterium prausnitzii* and *Roseburia* abundances compared with a control diet (Meslier et al., 2020). *F. prausnitzii* and *Roseburia* were also among taxa identified by random forest models that could best predict dietary adherence scores in a large, multicenter RCT involving older adults who consumed a Mediterranean diet for 12 months (Ghosh et al., 2020b). These taxa were positively associated with improved cognitive function and negatively associated with inflammatory markers and frailty (Ghosh et al., 2020b). Finally, in a prospective cohort study, long-term adherence to a Mediterranean diet was positively associated with *F. prausnitzii*, *Eubacterium eligens*, and *Bacteroides cellulosilyticus* (Wang et al., 2021). This study further showed individuals with a lower abundance of *P. copri* and high adherence to a Mediterranean diet had reduced risk of myocardial infarction compared with those who did harbor *P. copri* (Wang et al., 2021). Recent microbiome research on the Mediterranean diet underscores its inclusion in dietary recommendations. Dietary patterns that resemble the Mediterranean diet, such as the dietary approaches to stop hypertension (DASH) diet, have been recommended in recently updated dietary guidelines (Dietary Guidelines Advisory Committee, 2020; Health Canada, 2019) and research is warranted on the role of the microbiome in mediating their health effects.

CONTROVERSIES OF HEALTHY EATING: CAN KNOWLEDGE OF DIET-MICROBE-HOST INTERACTIONS OFFER SOLUTIONS?

Although dietary guidelines have evolved to reflect newly available evidence and generally agree in their recommendations, controversies remain (Nestle, 2018). Here, we discuss how host-microbe interactions can provide insight to help resolve these controversies.

Red and processed meats

Red meat contains essential micronutrients and is an important high-quality protein source. However, most dietary guidelines recommend that it be consumed in moderation, while processed meats (meat that has been transformed through salting, curing, and smoking) are recommended to be avoided (Table 1). In the context of cancer prevention, these assessments are shared by the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund International (Neuhouser, 2020). Despite these consistent recommendations, a series of systematic reviews from 2019 concluded that adults should continue current red- and processed-meat intake, citing weak evidence of their links to adverse health outcomes (Johnston et al., 2019). This sparked contentious debate in the nutrition field (Neuhouser, 2020). The gut microbiome provides an additional perspective in this controversy.

Proteolytic fermentation by gut microbes in response to red and processed meats results in the production of potentially detrimental metabolites, such as ammonia, p-cresol, and hydrogen sulfide (Louis et al., 2014). Hydrogen sulfide is produced from fermentation of sulfur-containing amino acids by bacteria such as *Desulfovibrio* (Louis et al., 2014), and acts as a mucolytic agent that increases intestinal permeability in mice (Ijssennagger et al., 2015). This then permits heme, also found in red and processed meats, to increase hyperproliferation and hyperplasia in the gut, inhibit tumor-suppressor genes, and activate oncogenes, all of which are potential causes of carcinogenesis (Ijssennagger et al., 2015). Antibiotic administration suppressed these effects in mice, suggesting a causal role for gut microbiota. In humans, sulfide-producing bacteria and pathways have been strongly associated with late-stage colorectal cancer (Yachida et al., 2019).

Gut microbes convert L-carnitine and phosphatidylcholine, which is present in high levels in meat products, into trimethylamine, which is oxidized by hepatic flavin-containing monooxygenases (FMOs) to trimethylamine-*N*-oxide (TMAO) (Zeisel and Warrier, 2017). TMAO circulates in plasma and is efficiently excreted by the kidneys and has been causally implicated in cardiovascular disease in animal models (Wang et al., 2011; Zhu et al., 2016). Observational studies have reported strong positive correlations between TMAO levels and cardiovascular disease risk (Zeisel and Warrier, 2017). However, animal experiments have been inconsistent (Aldana-Hernández et al., 2021; Koay et al., 2021), and TMAO levels in humans are often confounded and potentially caused by reduced kidney function (Zeisel and Warrier, 2017). Further, the TMAO paradigm does not align with epidemiological findings linking fatty fish, which is rich in TMAO and its precursors, with beneficial cardiometabolic outcomes (Alhassan et al., 2017; Jiang et al., 2021). The findings are further complicated by foods other than meat (i.e., cruciferous vegetables) that can inhibit FMO3 activity (Cashman et al., 1999). To elucidate causal contributions of TMAO derived from meat products, controlled-feeding trials in humans of sufficient duration that assess validated surrogate markers of cardiovascular disease are required.

Processed meats contain additional compounds not present in lean red meat that are likely to amplify microbiome-mediated detrimental effects. Most processed meats are high in saturated fat, which stimulates hepatic bile acid secretion in the small intestine (Ocvirk and O'Keefe, 2021). Some primary bile acids escape enterohepatic recirculation and enter the large intestine where they are transformed by microbes to secondary bile acids (Winston and Theriot, 2019). Of those, deoxycholic and lithocholic acids can cause oxidative stress and DNA damage and have been implicated in colonic carcinogenesis (Ocvirk and O'Keefe, 2021). A meta-analysis identified that in patients with colorectal cancer gut microbiome functional profiles were

characterized by elevated production of secondary bile acids (Wirbel et al., 2019), while a systematic review implicated saturated fats in the decrease of microbial richness and diversity (Wolters et al., 2019). Additionally, the curing agents used in processed meats, nitrate and nitrite, constitute substrates for microbial biotransformation to *N*-nitroso compounds (Kobayashi, 2018), which induce alkylating DNA damage and are, therefore, carcinogenic (Hebels et al., 2009).

Given the points made above, the toxicity of microbial metabolites produced from red and processed meats in the gut are relevant in interpreting their health effects (Figure 2). Although there is evidence that red meat constitutes a risk factor for colon cancer (Clinton et al., 2020), metabolites resulting from protein fermentation (e.g., hydrogen sulfide and ammonia) are of lower toxicity and not currently classified as human carcinogens (American Cancer Society, 2019). In contrast, microbial metabolites derived solely from processed meats (*N*-nitroso compounds and secondary bile acids) are of higher toxicity and carcinogenic (Ajouz et al., 2014; American Cancer Society, 2019). Given likely dose-response relationships, toxicological considerations justify the risk classification by the IARC/WHO expert panel for red meat (group 2A, probable carcinogen) and processed meats (group 1, carcinogen) and current dietary guidelines: moderate consumption of lean red meat and avoidance of processed meat.

Dairy products

There has been a longstanding controversy regarding the degree to which dairy products should be included in a healthy diet. On one hand, they are main dietary sources of calcium, phosphorus, and vitamin D when fortified. On the other hand, concerns have been raised about the saturated fat present in dairy products. There has been an emphasis on reducing the amount of fat consumed from dairy products, which is still reflected in most dietary guidelines that recommend skimmed and low-fat (0%–2%) dairy products (Comerford et al., 2021) and avoidance of high-fat (>25%) dairy products (e.g., certain cheeses, cream-based products, and butter). However, there is no consensus on full-fat dairy products (~3.5%), which are discouraged in some dietary guidelines (Table 1), although their detrimental effects have been questioned (Hirahatake et al., 2020).

Interactions between dairy fat and the gut microbiome are relevant to this discussion. A pioneering study showed that milk-derived saturated fats induced taurine-conjugated bile acids that promoted a bloom of the hydrogen-sulfide-producing pathobiont *Bilophila wadsworthia*, which triggered colitis in genetically susceptible mice (Devkota et al., 2012). Another study in mice corroborated these findings, where a high-fat diet predominantly derived from milk fat increased *B. wadsworthia* abundance and cecal bile acid levels, which induced gut barrier dysfunction and metabolic syndrome (Natividad et al., 2018). These mechanistic animal models highlight the potentially detrimental effects of milk-derived saturated fats on microbiome homeostasis, supporting dietary guidelines that suggest limiting consumption of high-fat dairy products (Figure 2). To our knowledge, well-controlled human intervention trials that evaluate whether levels of saturated fat in full-fat dairy products impact the microbiome are lacking, and such research is warranted to inform future dietary guidelines.

Low-fat versus low-carbohydrate diets

Although not covered in current dietary guidelines, the debate as to whether limiting either fat or carbohydrate intake would support optimal health had a substantial impact on previous dietary recommendations, such as the "Dietary Goals for the United States" from 1977 that recommended low-fat diets for all (Mozaffarian et al., 2018). The epidemic of obesity and other chronic diseases suggests that implementing these recommendations was not successful (Ludwig et al., 2021). The debate on low-fat versus low-carbohydrate diets remains highly relevant due to widespread popularity of the diets among the lay public. In several studies, low-carbohydrate diets were more effective for short-term weight loss compared with low-fat diets (Chawla et al., 2020), even when given *ad libitum* and compared with a calorie-restricted low-fat diet (Shai et al., 2008). However, scientists remain torn as to which diet, if either, is "superior"—see the carbohydrate-insulin model versus energy-balance model debate (Ludwig et al., 2021; Speakman and Hall, 2021)—also given that the long-term effects of these diets on weight loss do not seem to differ (Gardner et al., 2018).

The microbiome may contribute to the metabolic differences of low-fat versus low-carbohydrate diets. Insulin metabolism and weight gain in mice is impacted by gut microbiota in the context of high-fat, high-carbohydrate western diets (Bäckhed et al., 2007), and microbiota changes correlate with distinct metabolic and physiological effects of low-fat and low-carbohydrate diets in humans (Rondanelli et al., 2021). However, in humans, it is unknown if the microbiome causally contributes to the immediate metabolic effects of low-carbohydrate and low-fat diets. More is known about how these diets influence microbiome metabolism in relation to long-term effects on health. Low-fat diets are often rich in vegetables, fruits, whole grains, and plant-based proteins and therefore provide beneficial dietary components that alter microbiome metabolism, as discussed above. In contrast, low-carbohydrate diets are often high in fat and/or protein and, consequently, lower in fiber, which results in production of metabolites detrimental to colonic health. This was confirmed in an RCT in which a high-protein and low-carbohydrate diet increased concentrations of *N*-nitroso compounds and decreased levels of butyrate and anti-inflammatory phenolic compounds (Russell et al., 2011). In a separate study, a higher-fat, low carbohydrate diet caused unfavorable changes in gut microbiota, fecal metabolomic profiles, and plasma proinflammatory mediators in healthy young adults (Wan et al., 2019). These findings raise concerns about the long-term health outcomes of low-carbohydrate diets, and concur with a meta-analysis of prospective cohort studies showing mortality risk was highest in participants who consumed animal-based low-carbohydrate diets (Seidelmann et al., 2018). Therefore, there is rationale to improve low-carbohydrate diets through microbiome-targeted approaches (see below—targeted microbiome modulation).

APPLICATION OF THE GUT MICROBIOME TO ADVANCE NUTRITIONAL STRATEGIES

Contemporary national dietary guidelines are highly consistent and align with our understanding of how diet impacts microbiome-host interactions relevant to health. This congruence is

remarkable as the observational and intervention studies that substantiated dietary guidelines did not consider the microbiome. This points to the gut microbiome as a key mediator in physiological effects of diet, a function that might be evolutionarily rooted given that central aspects of mammalian anatomy, physiology, immunity, and metabolism have been shaped throughout evolution by diet-microbe-host interactions (Dominguez-Bello et al., 2019).

Although agreement between the nutrition and microbiome disciplines largely validates current dietary guidelines, we argue that more systematic incorporation of knowledge on the molecular foundations by which nutrients influence host-microbe interactions has the potential to enhance and innovate human nutrition. Below, we outline opportunities where a microbiome perspective could advance nutritional strategies and then propose a research framework that integrates the gut microbiome for their experimental validation.

Evolutionary considerations

Some of the most convincing support for the hypothesis that humans and their gut microbiota co-evolved is derived from the interpretation of the functional characteristics of human milk oligosaccharides (HMOs). Although HMOs are the third largest component of breast milk, they provide no direct energetic support to infants (Engfer et al., 2000). They do, however, enrich for beneficial gut microbes, such as bifidobacteria, that possess specialized genetic capabilities to utilize HMOs (Zivkovic et al., 2011) and have immunological effects in early development (Henrick et al., 2021; Tobias et al., 2022). Exclusive breastfeeding for the first 6 months of life is recommended by international scientific organizations for optimal infant nutrition and is strongly supported by observational studies that established the beneficial health effects of breastfeeding (Yan et al., 2014). Therefore, breastmilk constitutes a paradigm on the importance of evolutionary relationships among diet, microbiome, and human health.

Could this paradigm be extended to other aspects of nutrition? As humans, we have evolved with diets that are fundamentially different from industrialized diets (Sonnenburg and Sonnenburg, 2014). Although the exact characteristics of ancestral diets are unknown and likely varied seasonally and by location (Eaton and Konner, 1985), most ancestral diets contained more plants, higher dietary fiber, fewer refined carbohydrates and sugar, and an overall lower glycemic index (Konner and Eaton, 2010). Therefore, modern diets are likely evolutionarily mismatched with human physiology, which might be an important driver of the chronic disease epidemic (Cordain et al., 2005; Sonnenburg and Sonnenburg, 2019). Evolutionary considerations are, to some degree, already reflected in dietary guidelines, such as recommendations on high-fiber whole-plant foods and reducing the intake of refined and processed foods high in sugar, but it has been proposed that these attempts do not go far enough (Eaton, 2006).

Current recommendations of 25 and 38 g/day of fiber for females and males, respectively, (Institute of Medicine, 2006) do not match ancestral intakes of fiber estimated to be upward of ~100 g/day (Jew et al., 2009). The argument for higher intake is supported by a series of systematic reviews and meta-analyses suggesting fiber intake beyond 25–29 g/day would provide additional benefits (Reynolds et al., 2019). Human intervention studies testing ancestral fiber intake levels are rare. One feeding study wherein participants consumed over 100 g/day of fiber from a vegetable, fruit, and nut diet showed dramatically attenuated serum cholesterol levels and increased fecal SCFAs (Jenkins et al., 2001). In addition, a human trial in which African-Americans and rural South Africans (who habitually consume low- and high-fiber diets, respectively) had their diets swapped, resulting in decreased mucosal proliferation rates and colonic inflammation (biomarkers of colon cancer risk) in the African-Americans, while the Africans experienced reciprocal adverse changes in these measurements (O'Keefe et al., 2015). The effects of the diet swap correlated with opposing alterations in secondary bile acid abundance and SCFA production. Evolutionary consideration for how diet-microbiome interactions shaped human physiology could inform dietary recommendations, targeted nutritional strategies, and the development of food products to counter chronic disease risk (Deehan and Walter, 2016; Sonnenburg and Sonnenburg, 2019). Evolutionary considerations also lay the foundation for microbiome restoration strategies.

Microbiome restoration strategies

Industrialization has caused an increase in noncommunicable chronic diseases (Cordain et al., 2005) and a depleted microbiome characterized by reduced microbial diversity, diminished enzymatic capacity for carbohydrate utilization, reduced fermentation, and enrichment of mucus-degrading organisms (Sonnenburg and Sonnenburg, 2019). Although it will likely be impossible, and perhaps not advisable, to return microbiomes to their ancestral states, there is heightened interest in the development of microbiome restoration strategies that re-establish health-related functional characteristics (Sonnenburg and Sonnenburg, 2014). Such a strategy is supported by findings in a human intervention study that tested a diet rich in whole-plant foods (providing ~45 g of fiber daily), which elevated SCFA production and increased relative abundances of glycan-degrading carbohydrate active enzymes (Wastyk et al., 2021).

Microbiome restoration approaches focused solely on dietary fiber are unlikely to replenish lost microbial species (Sonnenburg and Sonnenburg, 2014). Proposals have been made to reintroduce taxa lost due to industrialization (volatile and/or associated negatively with industrialized societies of humans [VANISH]) (Sonnenburg and Sonnenburg, 2019). Although a promising approach in the longer term, many VANISH species have unknown pathogenicity, which makes their translation into nutritional strategies challenging. An alternate approach could be fermented foods, defined as foods produced through desirable microbial growth and enzymatic conversions of dietary components that, as a result, often have enhanced nutritional properties (Marco et al., 2021). Examples of fermented foods are kefir, yogurt, kombucha, tempeh, sauerkraut, and kimchi. Fermented foods are ranked highest among current diet trends and enjoy substantial popularity globally. If served uncooked, fermented foods often contain a high number of live microbes that have a long history of safe consumption (Marco et al., 2021).

Although persistence of most food microbes is only temporal due to their allochthonous nature in the human gut ecosystem (Walter, 2008; Walter et al., 2001), organisms from fermented

foods are well represented in human fecal microbiota (Bello et al., 2003; Pasolli et al., 2020). The benefits of fermented foods have been summarized by a qualitative systematic review that assessed both observational and experimental studies, which reported that yogurt, kefir, and other fermented milks were associated with favorable outcomes in gastrointestinal health, risk of type 2 diabetes and cancer, and weight management (Savaiano and Hutkins, 2021). Further, a large observational study in over 120,000 participants identified a significant inverse association between weight gain and yogurt consumption (Mozaffarian et al., 2011). However, evidence from RCTs is extremely sparse, and fermented foods are just beginning to be recommended in dietary guidelines (Table 1). An RCT that tested a diet including ~6 servings of fermented foods daily increased microbiome diversity and reduced several proinflammatory cytokines and chemokines (Wastyk et al., 2021). Additional well-designed RCTs are needed with validated surrogate endpoints to justify the inclusion of fermented foods in dietary recommendations. Such research should consider that detrimental nutritional aspects of some fermented foods (e.g., fermented sausages, some cheeses, and sugar-sweetened yogurts), such as high amounts of salt, saturated fat, sugar, and curing agents, might outweigh potential benefits from live microbes.

In theory, a microbiome restoration strategy could also be accomplished with dietary probiotics and synbiotics (a combination of probiotics and prebiotics). There is a large body of research exploring these strategies in a number of clinical settings, and different mechanisms are proposed such as their immunomodulatory effects (Hill et al., 2014). If bacterial strains autochthonous to the human gastrointestinal tract are used, probiotics can successfully colonize for extended periods (Maldonado-Gómez et al., 2016). Such a strategy could diversify the microbiome but this, to our knowledge, has not been systematically tested. Nevertheless, a proposal has been made to explore dietary recommendations for daily intake of live microbes for health promotion (Marco et al., 2020). For this concept to become viable, epidemiological studies and RCTs that test the value of probiotics in the prevention of chronic diseases are required.

Reformulation of processed foods

Although dietary guidelines recommend their avoidance (Table 1), processed foods contribute substantially (>50%) to daily energy intake in many parts of the world, such as the United States and United Kingdom (Marino et al., 2021). Their popularity is driven by factors such as marketing exposure, convenience, and their low price (Baker et al., 2020). To improve population-wide diet quality, reformulation instead of elimination of processed foods has been proposed (Tobias and Hall, 2021). Such attempts will require innovation in food engineering that would benefit from considerations of diet-microbe-host interactions. For example, white flour in food products could be partially replaced with indigestible fermentable starches and other fibers, thereby altering the inherent characteristics of processed foods (e.g., fiber content, glycemic index, and nutrient digestibility) to offset detrimental effects on both gut microbiota and host metabolism (Deehan and Walter, 2016). This approach has already been suggested to have wide-reaching implications in a statistical modeling study, which predicted over 70% risk reduction in type 2 diabetes and cardiovascular disease if 50% of the market share of processed foods in the United Kingdom were fortified with ~3 g of fiber (Canene-Adams et al., 2022). Similar approaches could be applied to reintroduce other bioactive compounds such as phytochemicals, potentially in tandem with dietary fibers. Instead of relying on individuals to change their eating behaviors to improve their health, which has a limited success rate (Patnode et al., 2017), a greater availability of reformulated processed foods may enable individuals to improve their diet quality without significantly changing dietary habits.

Targeted microbiome modulation

Although it is difficult to define what constitutes a 'healthy' microbiome (McBurney et al., 2019), specific taxa and functional characteristics of the gut microbiome, specifically those influenced by diet (e.g., health-relevant SCFAs and secondary bile acids), have been linked to health outcomes (Salosensaari et al., 2021). Once health-promoting taxa and microbiome characteristics are identified, they could be targeted with nutritional strategies. For example, metabolically detrimental low-carbohydrate or high-meat diets (Russell et al., 2011) could be supplemented with fermentable fibers to shift microbial metabolism from protein to carbohydrate fermentation, improve gut barrier integrity, and induce systemic metabolic benefits through SCFAs (Makki et al., 2018). Given the independent metabolic effects of dietary fiber (Wanders et al., 2011) and low-carbohydrate diets (Chawla et al., 2020), their combination could potentially generate synergy.

Targeted use of dietary fiber could also be envisioned to enhance putative health-promoting organisms and their metabolic outputs. This approach essentially aligns with the concept of prebiotics, which are defined as substrates that are selectively utilized by host microorganisms, conferring a health benefit (Gibson et al., 2017). Unfortunately, this definition does not provide clear guidance on what constitutes a "selective" effect, how such effects can be causally linked to health benefits, and how to differentiate prebiotics from dietary fibers (Deehan et al., 2017). These concerns led to the European Food Safety Authority to rule that prebiotics cannot be labeled as such but must be labeled as dietary fibers (Delcour et al., 2016). There is also no mention of food-derived prebiotics in national dietary guidelines (Table 1), which is unfortunate as the overall concept of targeted microbiome modulation is promising. Hamaker and Tuncil proposed a conceptual framework whereby application of dietary fibers containing discrete structures (defined as *"a unique chemical structure…which aligns with encoded gene clusters in bacterial genomes"*) could be used to obtain predictable and desirable changes in microbiota composition (Hamaker and Tuncil, 2014). This framework was experimentally tested in a human trial, in which subtle structural differences in type IV resistant starches directed SCFA outputs toward either propionate or butyrate, which have distinct metabolic and physiological functions (Deehan et al., 2020). There is tremendous promise in targeted nutritional microbiome modulation for both dietary guidelines and therapeutic foods, but questions remain regarding what aspects of the microbiome should be targeted, and RCTs are required to demonstrate if such strategies translate into improved health outcomes.

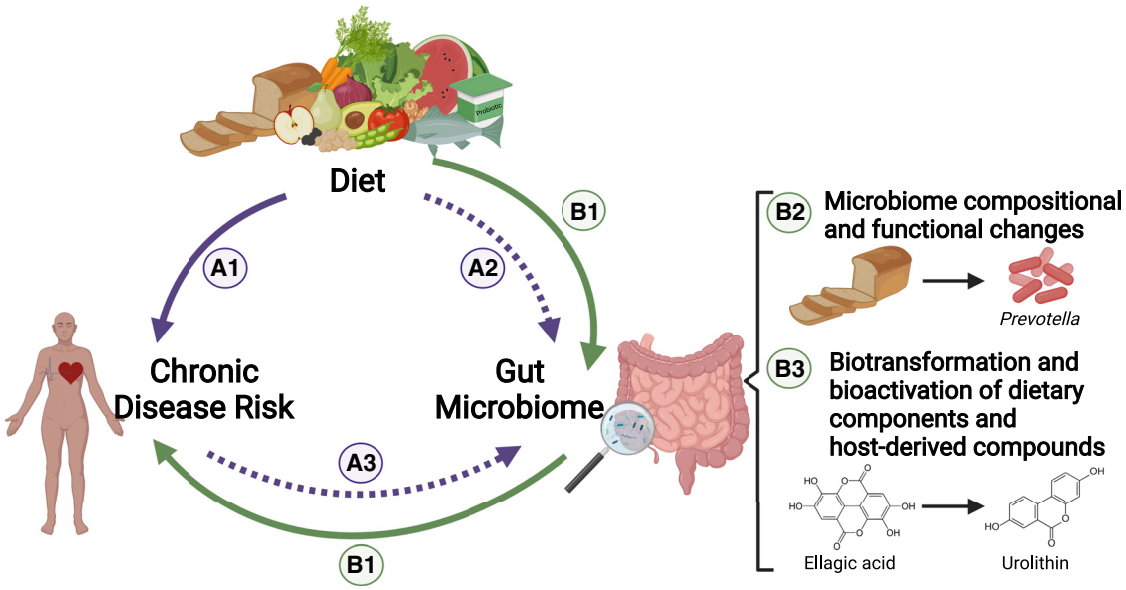

Figure 3. The complex, multidirectional cause-and-effect interrelationships among diet, the gut microbiome, and human health
Diet can influence human health both directly and independently of the microbiome (A1). Even without a causal contribution of the microbiome, the physiological effects of diet can be correlated with microbiome shifts due to independent parallel effects of diet (A2) or due to diet-induced physiological changes in the host altering the microbiome (A3). In contrast, the microbiome can mediate the health effects of diet (B1), either by diet altering the composition and function of the microbiome (B2), or through microbial biotransformation and bioactivation of dietary components (e.g., phytochemicals) and diet-induced host-derived compounds (e.g., bile acids) (B3).

Precision nutrition

Even well-controlled dietary interventions can elicit variable effects across individuals (Gardner et al., 2018), which questions the one-size-fits-all approach currently applied in dietary guidelines. The emerging area of precision nutrition (also referred to as "personalized nutrition") aims to instead leverage human individuality to first identify which person-specific features predict responses to dietary interventions, then tailor nutrition recommendations accordingly to achieve the same responses in different people (Ordovás et al., 2018). Given the highly individualized response of gut microbiota to diet (Guthrie et al., 2021; Johnson et al., 2019), microbiome measurements are a key component of precision-nutrition strategies targeted toward chronic disease prevention and treatment, among other person-specific factors (e.g., genetics, baseline metabolism, and physical activity). Machine-learning approaches can be applied to large participant cohorts to identify which features predict health outcomes. For example, machine-learning algorithms accurately predicted postprandial glycemic responses to standardized meals using participant data on blood parameters, dietary habits, microbiome composition, and other factors (Berry et al., 2020; Zeevi et al., 2015). Such predictions can benefit from the combination of microbiome and host genetic data, as shown in a study in which high baseline *Prevotella*/*Bacteroides* ratios could predict greater weight loss in subjects with low salivary-amylase gene copy numbers in response to a diet high in dietary fiber, whole grains, fruit, and vegetables (Hjorth et al., 2020).

National dietary guidelines currently do not consider precision or personalized approaches, and their implementation will be challenging on a population scale. However, technology to do so exists and could capitalize on a combination of microbiome sequencing and the use of smartphone apps for dietary surveillance, ultimately providing high-dimensional data for machine-learning algorithms to communicate personalized nutrition recommendations back to users (Zmora and Elinav, 2021). Multicenter validation of predictive models must be conducted in diverse populations (including non-western and developing countries) to determine their broad applicability and to encourage further refinement. Precision-nutrition approaches will depend on continued collaboration between nutrition and microbiome disciplines, and their population-wide implementation will require significant additional input from regulatory bodies, professional societies, and policymakers.

A way forward

Information on diet-microbiome-host interactions has the potential to further validate, refine, and innovate dietary recommendations. To be meaningful, integration of the gut microbiome into dietary guidance requires evidence of mechanistic and causal contributions of the microbiome in the physiological effects of diet. Establishing causality for the gut microbiome's role in the predisposition to human diseases remains a challenge (Walter et al., 2020), and this is further complicated in nutritional studies (Wilkinson et al., 2021) as the interactions between diet, gut microbiota, and human health are complex and multidirectional (Figure 3). Human studies assessing the role of the microbiome in nutrition are further complicated by the complex ecological characteristics of the microbiome (interindividual, geographic, and temporal variability) and limitations of nutritional studies that even apply to RCTs (e.g., difficulty of assessing dietary intake and adherence to study protocols, collinearity of diet components, and confounders) (Wilkinson et al., 2021). These complexities must be considered in the design of future nutrition research to elucidate what factors, including the microbiome,

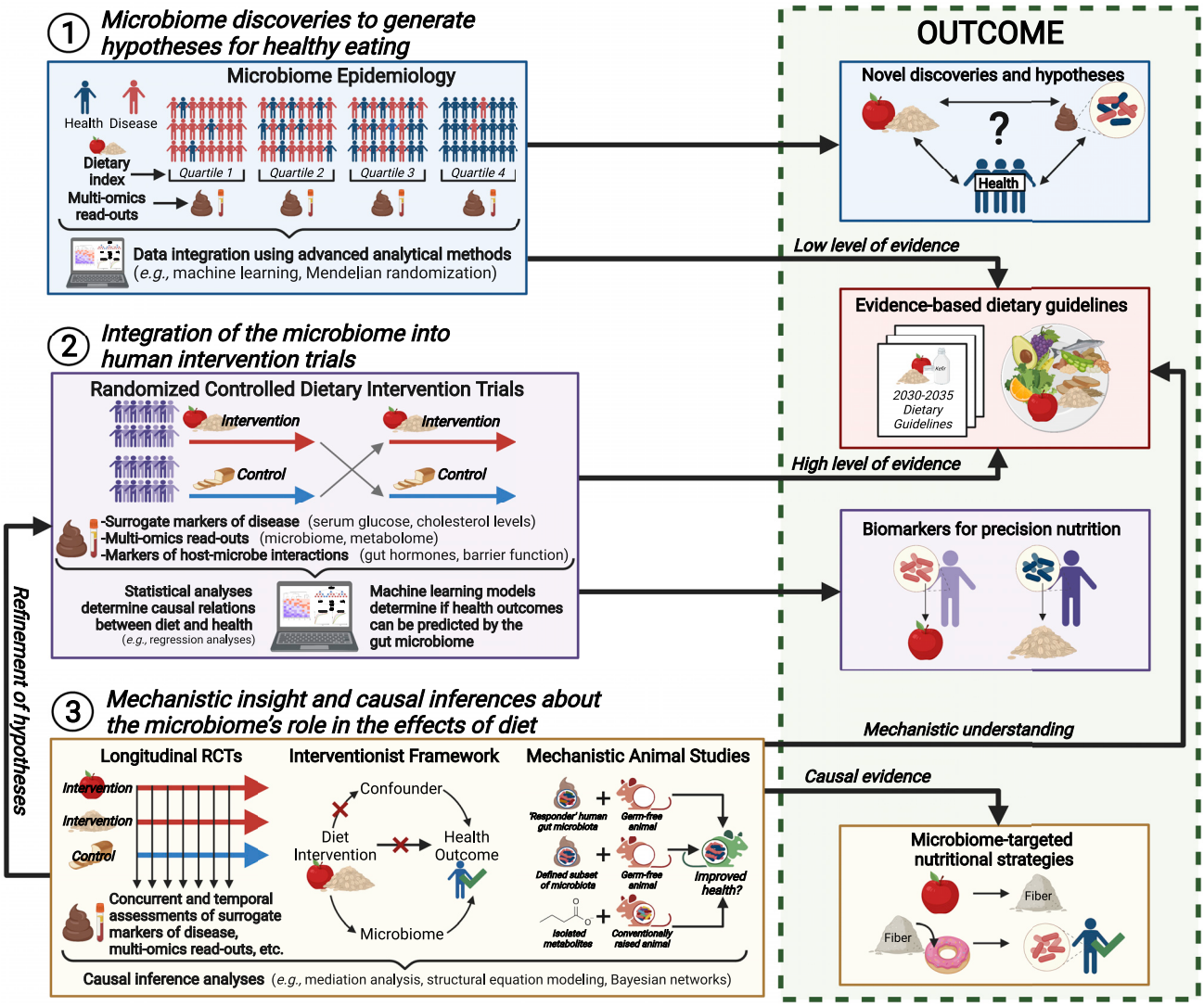

Figure 4. An experimental framework that integrates the gut microbiome into all stages of nutrition research to advance understanding of the microbiome's role in healthy eating

(1) Microbiome epidemiology can elucidate associations between the microbiome, diet, and diet-induced physiological effects. Such information cannot assign causality but can aid discovery and hypothesis generation, as well as contribute to the evidence base for dietary guidelines.

(2) RCTs can determine the causal relationship between diet and health and provide strong evidence that can directly inform dietary guidelines. If combined with multi-omics microbiome-based analyses, this research can identify microbial biomarkers for precision-nutrition strategies. However, causal inferences for the microbiome's role in the effects of diet are still difficult to achieve.

(3) Human intervention studies can be specifically designed to determine cause-and-effect relationships when combined with appropriate statistical approaches (e.g., mediation analysis). Causality and underlying mechanisms can further be established in animal models. Causal and mechanistic information provide additional layers of evidence for dietary guidelines and the development of targeted nutritional strategies. RCTs, randomized controlled trials.

mediate the health effects of diet. We refer readers to excellent reviews that outline best-practice guidelines for diet-microbiome research (Johnson et al., 2020; Klurfeld et al., 2018; Shanahan et al., 2021), and we extend these with an experimental framework using three pillars that integrates the gut microbiome into all stages of nutrition research (Figure 4).

Microbiome discoveries to generate hypotheses for healthy eating

The gut microbiome can inform nutrition beyond the validation of established dietary strategies and can contribute to the identification of microbiome features as future nutritional targets. "Microbiome epidemiology" using large population-wide observational studies (Wilkinson et al., 2021) have already identified associations between the gut microbiome and human disease states (Falony et al., 2016; Jackson et al., 2018). Multi-omics technologies (e.g., metagenomics, metaproteomics, metabolomics) and the use of advanced analytical methods such as machine learning (Mars et al., 2020; Mills et al., 2022), mediation analysis (Chen et al., 2021; Patrick et al., 2020), and Mendelian randomization (Liu et al., 2022; Qin et al., 2022), have established potential mechanistic and causal foundations that underpin biological pathways. Recent studies have extended this framework

and combined microbiome and nutritional epidemiology to elucidate the involvement of the microbiome in diet-induced physiological effects (Asnicar et al., 2021; Wang et al., 2021). Although such observational studies cannot assign causality, high-quality, large-scale cohort studies contribute to the evidence base for dietary guidelines (Williams et al., 2020). Combining nutrition and microbiome epidemiology allows for the discovery of connections among the microbiome, health, and specific diets or dietary components. The underlying mechanisms and biological plausibility of these interactions and their value as nutritional targets and diagnostic markers can then be confirmed in experimental systems.

Integration of the microbiome into human intervention trials

RCTs are the gold standard in nutrition for establishing causality in humans (Lichtenstein et al., 2021) and, if they are performed well, are higher in the evidence hierarchy than observational trials. We argue that this hierarchy also applies to microbiome studies. Nutritional RCTs can be extended with the same multi-omics approaches applied in microbiome epidemiology to integrate the gut microbiome and effectively test specific diet-microbiome interactions. Surrogate markers that are valid predictors of disease risk can be combined with microbiome endpoints (e.g., compositional shifts, functions, and metabolites) and molecular markers of biological processes hypothesized to link metabolic activities of the gut microbiome with host immunometabolism (i.e., gut hormones, cytokines, TMAO, and intestinal-barrier integrity markers) to confirm findings from epidemiological studies and provide putative mechanistic explanations (Deehan et al., 2022).

Crossover designs have advantages for RCTs with microbiome endpoints as participants serve as their own controls, which allows for the removal of interindividual variation of person-specific factors (e.g., microbiome, genetics, metabolite profiles, and baseline clinical measurements) (Lichtenstein et al., 2021). Studies should further control for other confounding variables, such as demographic (age and sex) (de la Cuesta-Zuluaga et al., 2019; Ghosh et al., 2020a) and lifestyle factors (habitual diet and medication use) (Bowyer et al., 2018; Jackson et al., 2018). In this context, stool consistency and alcohol consumption have been identified as unexpected confounders (Vandeputte et al., 2016; Vujkovic-Cvijin et al., 2020). Stratified randomization should be used to balance participant allocation to treatment groups based on factors such as age and sex, and detailed information should be collected on relevant confounding variables so they can be controlled for in statistical analyses. The substantial confounder of habitual diet can be removed through sufficiently controlled-feeding studies in free-living or domiciled participants in which all foods are provided, including a sufficient run-in period (Lichtenstein et al., 2021). Such studies are difficult and expensive to conduct but have already been applied successfully in the microbiome field (Guthrie et al., 2021; Holscher et al., 2018b).

Intervention trials can assign causality to the health effects of diet and therefore directly inform dietary guidelines (Lichtenstein et al., 2021). If the microbiome is integrated, RCTs also provide putative mechanistic explanations for the role of the microbiome in the health effects of diet (Deehan et al., 2022) and diagnostic microbiome-based biomarkers for precision-nutrition strategies (Berry et al., 2020; Zeevi et al., 2015). Regression and correlation analyses can be applied to determine associations between diet-induced changes in microbiome composition/functionality and clinical and mechanistic endpoints (Meslier et al., 2020; Vijay et al., 2021). Additionally, machine-learning models can determine if diet-induced physiological changes can be predicted by effects on the microbiome or biological processes in the host impacted by the microbiome (Ghosh et al., 2020b; Nielsen et al., 2020). However, unless these trials and analyses are extended with specific experimental and statistical approaches, they cannot establish the causal role of gut microbiota in the effects of diet (see below).

Mechanistic insight and causal inferences about the microbiome's role in the effects of diet

Longitudinal data can be collected in RCTs to allow for causal inference since causes must temporally precede effects (Gelfand et al., 2009) using approaches such as mediation analyses (Leong et al., 2018; Vijay et al., 2021). Other mathematical approaches, such as structural equation modeling (Rath et al., 2021) and Bayesian networks (Dao et al., 2016), can also disentangle cause-effect relationships among diet, the microbiome, and human health. Arguably, the most promising experimental design for causal inference directly in humans is the "interventionist framework," where cause-and-effect relationships are inferred when an intervention directed at a putative cause elicits a favorable effect (Lynch et al., 2019). This approach could be adapted to dietary interventions with well-characterized effects to test if targeting microbiome features or giving microbial metabolites (the putative cause) elicit the predicted effect (Walter et al., 2020).

Human studies can be extended with animal models to establish the causal role of the microbiome, identify the causal components among the microbiome, and determine underlying mechanisms (Walter et al., 2020). Specific microbes, either alone or as communities (gnotobiotic animals), or microbial metabolites that correlate with physiological effects of human dietary interventions can be tested in germ-free animal models of disease (Round and Palm, 2018). Gnotobiotic animals allow for the removal or addition of specific microbes to determine causal components within microbial communities and can be challenged with feeds that mimic the human diet. Human microbiota-associated (HMA) rodents, in which human fecal microbiota are transplanted into rodent models of disease, are the most commonly used and complex model to establish causality of the microbiome (Walter et al., 2020). HMA animals can be extremely powerful to compare human microbiomes that respond or do not respond to diet interventions, especially if the hypothesis is that differences are caused by the presence or absence of specific microbes (Gehrig et al., 2019; Kovatcheva-Datchary et al., 2015). However, HMA animals have substantial limitations in making causal inferences regarding diet-induced compositional changes of the human microbiome (Arrieta et al., 2016). Diets that do not provide live microbes are unlikely to add or remove microbial species from the microbiome but only alter relative proportions within the community (Deehan et al., 2017). Such changes are unlikely to be replicated in recipient animals given that ecological and evolutionary forces shaping the microbiome are distinct from those in the donor (Arrieta et al., 2016; Walter et al., 2020).

Despite their limitations, animal models, especially if their microbiomes are well-controlled and combined with multi-omics approaches, have the ability to complement human studies in that they establish mechanistic foundations of the effects of diet. Such studies could be further improved with the use of animals that are better mimics of human physiology, such as pigs and primates (Dhakal et al., 2019; Nishida and Ochman, 2019). Although insight from mechanistic and causal studies is not required to establish and confirm health effects of dietary components or the utility of microbiome-based biomarkers, it is invaluable for the refinement of hypotheses that can innovate the development of targeted nutritional strategies and provide additional layers of evidence for dietary recommendations.

CONCLUDING REMARKS

Diet is strongly connected to the presence or absence of disease, which is in turn linked to the microbiome. The gut microbiome may constitute the "black box" of nutrition research, and diet-microbiome interactions likely contribute to the mechanistic foundation of the physiological effects of diet. There is strong biological and evolutionary justification for the two fields to extend already active and ongoing collaborations to deepen our understanding of how to optimize health with diet. Microbiome-focused endpoints should be embedded within all aspects of nutrition science to strengthen the evidence base for dietary guidelines. Nutritional microbiology studies have potential to holistically inform aspects of healthy eating and thus contribute to the solution of diet-related disease prevention and management.

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DECLARATION OF INTERESTS

E.C.D. is an employee of AgriFiber Solutions LLC, a manufacturer of upcycled dietary fibers and prebiotics. C.J.F. provides scientific advice to Dairy Farmers of Canada and serves on the scientific advisory board for ByHeart. C.M.P. reports receiving honoraria and/or paid consultancy from Abbott Nutrition, Nutricia, Nestlé Health Science, Fresenius Kabi, Pfizer, and funding from Almased Wellness GmbH. J.W. has received honoraria and/or paid consultancy from Novozymes, Nestlé, and ByHeart and reports research funding from industry sources involved in the manufacture and marketing of prebiotics and dietary fibers. J.W. is further a co-owner of Synbiotic Health, a developer of synbiotic products. All other authors declare no competing interests.

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