Food for thought: Making the case for food produced via regenerative agriculture in the battle against non-communicable chronic diseases (NCDs)

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ABSTRACT

Non-communicable diseases (NCDs) pose a global health challenge, leading to substantial morbidity, mortality, and economic strain. Our review underscores the escalating incidence of NCDs worldwide and highlights the potential of regenerative agriculture (RA) products in mitigating these diseases. We also explore the efficacy of dietary interventions in NCD management and prevention, emphasizing the superiority of plant-based diets over those high in processed foods and red meat. Examining the role of the gut microbiome in various diseases, including liver disorders, allergies, metabolic syndrome, inflammatory bowel disease, and colon cancer, we find compelling evidence implicating its influence on disease development. Notably, dietary modifications can positively affect the gut microbiome, fostering a symbiotic relationship with the host and making this a critical strategy in disease prevention and treatment. Investigating agricultural practices, we identify parallels between soil/plant and human microbiome studies, suggesting a crucial link between soil health, plant- and animal-derived food quality, and human well-being. Conventional/Industrial agriculture (IA) practices, characterized in part by use of chemical inputs, have adverse effects on soil microbiome diversity, food quality, and ecosystems. In contrast, RA prioritizes soil health through natural processes, and includes avoiding synthetic inputs, crop rotation, and integrating livestock. Emerging evidence suggests that food from RA systems surpasses IA-produced food in quality and nutritional value. Recognizing the interconnection between human, plant, and soil microbiomes, promoting RA-produced foods emerges as a strategy to improve human health and environmental sustainability. By mitigating climate change impacts through carbon sequestration and water cycling, RA offers dual benefits for human and planetary health and well-being. Emphasizing the pivotal role of diet and agricultural practices in combating NCDs and addressing environmental concerns, the adoption of regional RA systems becomes imperative. Increasing RA integration into local food systems can enhance food quality, availability, and affordability while safeguarding human health and the planet's future.

1. Introduction

According to a 2020 WHO review, non-communicable diseases (NCDs) significantly contribute to worldwide mortality [1]. NCDs are defined as chronic diseases neither caused by infectious pathogens or injury nor by maternal, perinatal, or nutritional conditions. Genetic,

physiological, environmental, and behavioral factors combine to influence NCDs, which account for 71% of deaths worldwide [2]. The impact of NCDs on mortality and morbidity is observed in populations at all socioeconomic levels. Cardiovascular disease (atherosclerotic heart disease and stroke) is the most significant contributor, followed by cancer, chronic respiratory diseases, and diabetes mellitus. Lifestyle is

considered a critical factor in pathogenesis, with unhealthy diets, excessive tobacco and alcohol use, and poor exercise habits increasing the risk of death. As such, NCDs are a substantial concern from an economic standpoint, increasing expenditures necessary in both primary and secondary prevention, as well as palliation of the consequences of NCDs (Fig. 1).

Dietary manipulation has long been used to help treat NCDs, and numerous research studies confirm the role of diet in reducing type 2 diabetes mellitus, obesity, atherosclerosis-related cardiovascular disease, and other illnesses [3–7]. Perceived benefits were initially attributed to the nutrient content of the diet, leading to changes in the human

or animal metabolism after digestion and absorption. Further research demonstrates the connections between the diet's influence on the gut microbiome and its influence in managing NCDs [8].

This new insight raised questions regarding how we assess the nutritional content of food and whether we should be looking at this not only from the viewpoint of how it benefits human metabolism directly but also how it enhances the function of the gut microbiome, the role of which we now appreciate is critical to the meta-organism (the human body and its component microbes). For example, new methodologies assessing the food content of phytosterols are currently being developed [9,10]; however, their effect on the structure/function of the gut

Fig. 1. This infographic presents data from the World Health Organization on non-communicable diseases (NCDs) and how different behaviors affect the risk of developing NCDs. Substantial evidence supports the use of dietary manipulation in the treatment and prevention of NCDs.

microbiome remains largely unknown. Understanding the role of the thousands of different phytosterols is especially important, considering our current knowledge suggests that gut microbiota is an integral component of the meta-organism.

The importance of food in limiting the impact of NCDs appears unquestioned. However, the debate surrounding food quality based on production practices warrants further discussion. Industrial agricultural (IA) practices allow for large-scale human and animal food production, primarily focusing on efficiency and yield. However, there is growing evidence that IA methodologies have detrimental effects on the soil environment, including reduced biodiversity, increased air and water pollution, and contaminated food resulting from trace remnants of chemical inputs such as herbicides, pesticides, antibiotics, and hormones. Agricultural practices utilizing regenerative principles (regenerative agriculture [RA]) have been suggested to mitigate and correct some IA-related challenges. Moreover, there is developing evidence suggesting that the food produced by RA is of better nutritional quality, given that RA practices foster greater soil microbial diversity, benefitting the microbiota of plants and animals, including humans. Additional ecosystem benefits provided by RA practices will be explored further in this review.

We sought to evaluate the current evidence on how health is affected by the influence of diet on the gut microbiota. Moreover, we examined the importance of soil and plant microbiomes, agricultural methods (IA versus RA), and the resultant quality of food on the gut microbiome and, ultimately, on health.

2. The microbiome and liver disease

Nonalcoholic fatty liver disease (NAFLD) includes nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) and is associated with type II diabetes mellitus/metabolic syndrome and obesity [11]. The prevalence of NAFLD is estimated to be 24% worldwide [12]. Most individuals with NAFLD have minimal or no inflammation associated with steatosis (NAFL), yet 20–25% of all patients with NAFLD have NASH, wherein there are varying degrees of inflammation related to ballooning degeneration and cell death of hepatocytes. Increasing fibrosis and cirrhosis can result when the reparative capability of the liver is overwhelmed. Liver failure from NASH is the leading indication for liver transplant in the United States [13]. Therapy with medications has been disappointing, and the mainstay of treatment remains lifestyle modification, with reduced caloric intake and exercise being pivotal.

In the progression from normal to hepatic steatosis and transition to NASH, there is increasing evidence that the gut microbiome plays a role [14,15]. There are differences in the microbiome composition in obese versus non-obese individuals [16]. Recent research suggests that liver tissue microbiota (rather than just from the gut) may play a role in the development of NAFLD [17,18]. Proposed pathogenic mechanisms leading to NAFLD/NASH include enhanced extraction of fats from food, serving as an inflammatory stimulus, modulation of the innate immune system, regulation of bile acid turnover, changes in choline metabolism, and production of ethanol by the microbiota [15,19,20]. Based on this accumulating knowledge, treatment strategies based on microbiome manipulation are underway [21–23].

Alcoholic liver disease (ALD) has a histologic spectrum that is similar to NAFLD, with mild cases showing just steatosis and more severe disease associated with a similar pattern of steatohepatitis and ballooning degeneration/cell death, with progressive accumulation of fibrosis and eventually cirrhosis. As with NAFLD, medications have limited benefit in ALD, and therapy once again centers on lifestyle modification, primarily cessation of alcohol. Over the last several decades ALD has remained one of the top three reasons for liver transplants [13]. The gut microbiome also appears to play a significant role in the development and progression of alcoholic liver disease [14,24,25]. Proposed mechanisms of injury are common to both NASH and ALD, with some differences [20,25–28]. Ongoing trials are looking at the role of

microbiome manipulation in treating ALD [24–26].

3. Allergies, asthma and the microbiome

Asthma, as well as food and environmental allergies, have been increasing in prevalence and are a growing public health burden. This increase correlates with industrialization and is most pronounced in developed and rapidly developing countries [29,30]. Sensitization develops at surfaces such as the skin, lung, and mucosa of the aerodigestive tract, and the role of the microbiota in these locations has recently been the focus of much attention. The gut microbiome significantly affects the risks for asthma and allergies among genetically predisposed atopic individuals [31]. Prebiotic foods (e.g., dietary fiber, fruits, vegetables, and resistant starch) and probiotic foods (e.g., yogurt, kefir, kimchi, miso, pickles, sauerkraut, and tempeh) promote the growth and maintenance of *Bifidobacterium* species, some *Clostridia* species, and *Lactobacilli* [32]. Thus, these bacteria are more abundant among people with a plant-based diet from a diverse soil. *Bifidobacterium* species, some *Clostridia* species, and Lactobacilli are commonly associated with a reduced risk of allergies [33]. *Bifidobacteria* work to reduce allergies by enhancing gut barrier function and upregulating tolerance mechanisms in the GI tract that reduce inflammation [34]. *Bifidobacteria* and *Clostridia* species can stimulate the production of regulatory T cells (Tregs), thereby increasing anti-inflammatory cytokines like IL-10 and TGF-β [35]. *Bifidobacteria* and *Lactobacillius* species reduce Th2 cell activation, which produces IL-4 [36]. The IL-4 is part of the Type II response that is allergy-promoting. For example, IL-4 drives B-2 cells to produce IgE, which fuels allergic reactions. *Bifidobacteria*, some *Clostridia* species, and *Lactobacillus* species can modulate the immune response by producing short-chain fatty acids (SCFAs), such as butyrate, that alter signal transduction to favor tolerance [37]. Specifically, butyrate acts as a histone deacetylase inhibitor, promoting a more permissive chromatin structure for genes associated with Treg differentiation, such as FOXP3, CD25, CTLA-4, and IL-10.

Highly processed foods, high sugar intake, alcohol intake, inadequate fiber, and a general decrease in probiotic and prebiotic foods promote a gut flora high in *Staphylococcus aureus* and *Enterococcus faecalis* [38]. High concentrations of *Staphylococcus aureus* and *E. faecalis* increase the risk of food allergy. They do this primarily by disrupting the gut barrier [39]. The damaged enterocytes produce proinflammatory cytokines, including IL-33, IL-25 (IL-17E), and TSLP, that drive the immune system toward the Type II immune response typical of allergic reactions.

4. The microbiome and *Clostridium difficile* infection

Clostridium difficile is a significant cause of intestinal infection, especially after the use of antibiotics. This bacterium is a substantial cause of morbidity and mortality in both the hospital and outpatient setting. The organism is a normal component of the gut microbiota that is usually kept in check by other microbiota members. When this balance is disturbed, usually after the administration of antibiotics, there can be a proliferation of *Clostridium difficile.* Toxins produced by these bacteria cause damage to the colonic mucosa. Antibiotics, while effective in eliminating live *C. difficile,* also lead to further disruptions of the gut microbiota. This disruption, combined with the development of antibiotic resistance, can lead to treatment failure or recurrent infections. Probiotics, proprietary blends of bacteria thought to benefit the consuming native microbiota of individuals, are a mainstay of treatment.

Additionally, the use of Fecal Microbiota Transplant (FMT), which refers to the procedure wherein stool collected from a healthy donor is introduced into a patient's gastrointestinal tract, is very effective in managing antibiotic treatment failure and recurrent infections with marked improvement in gut bacterial diversity following transplant [40]. A recent small study suggested that FMT is an effective first-line

therapy for *Clostridium difficile* infection [41]. However, considering the FMT-associated dangers, such as transmission of infectious pathogens and traits for conditions like obesity and depression, among others, recent research that has focused on the use of 'synthetic' stool derived from cultures from the stool of healthy donors, seeks to overcome this obstacle [42,43]. A modified form of FMT is a newly FDA-approved product, SER-109. SER-109 is a cocktail of bacteria in pill form that can prevent recurring infections of *C. difficile* in people who have had previous episodes [44]. There also appears to be promise in using sterile stool filtrates [45], suggesting that microbiota metabolites are essential in the mechanism of action of this treatment modality.

5. The microbiome and inflammatory bowel disease

The term inflammatory bowel disease (IBD) encompasses two relatively distinct clinical entities: Crohn's disease (CD) and ulcerative colitis (UC). Whereas CD tends to be patchy in distribution, often transmural, and can affect anywhere in the gastrointestinal tract, UC only affects the colon mucosa, starting in the rectum and extending proximally to variable extents. As implied, a small subset of patients may have overlapping features. These diseases appear to be increasing in incidence and prevalence over time, which seems to correlate with an increase in industrialization and improvement in hygiene [46–49] but may be directly related to the nature and quality of the foods consumed [50]. The pathogenesis of IBD appears to involve an interplay between host genetic factors and microbial and environmental factors. In many ways, allergies and these autoimmune diseases are very similar; both involve a combination of genetic predisposition and the exposure of the host to the triggers that initiate disease. IBD is a disordered and poorly regulated immune-mediated inflammation in intestinal and extra-intestinal locations. Diet is considered a critical environmental factor given its proven role in the health and maintenance of the gut microbiota. Dysbiosis as a consequence of dietary factors can lead to abnormal development and/or functioning of the immune system in genetically susceptible individuals [51–54]. There is no available cure for these relapsing and remitting diseases. The current strategies for treatment revolve around suppressing the immune system by utilizing various biological and non-biologic medications. Even though this has led to better outcomes in the care of patients with IBD in recent years, there is still much room for improvement. The pivotal role of the gut microbiota's interplay with the host immune system, has generated great interest in modifying the content and composition of microbiota for treatment and possibly even prevention. To this end, dietary measures such as the Specific Carbohydrate Diet, probiotics, antibiotics, and Fecal Microbiota Transplant (FMT) all show promise [52,55–57].

6. The microbiome and colon cancer

Colorectal cancer ranks as a major global cause of cancer and cancer related deaths. Despite a gradual decrease in colon cancer-related deaths due to enhanced screening, it persists as the second most common cause of cancer-related fatalities for both men and women in the United States. [58]. Of some concern, despite this decrease in older individuals, there has been a trend of increase in incidence in younger individuals (under-50 and 50–64-year-old categories) [59]. Generational differences in environmental exposures, diet, and/or additional lifestyle factors are proposed as potential factors leading to the observed trends [60]. It has long been recognized that dietary factors play a role in the development of colorectal cancer, specifically, a diet rich in fruits and vegetables is protective, and red meat intake seems deleterious. Obesity is an independent risk factor [61].

Considering recent increases in our understanding of the relationship between gut microbiota and diet, future research should focus on the possible connections between colon cancer, diet, and the gut microbiome. There are apparent differences in the microbiome composition in patients with colorectal cancer and those with a tendency to

precancerous polyps compared with controls [62–64]. Moreover, we are increasingly aware that specific microbiomes can favor the function of specific anti-tumor treatments. For example, *Bacteroides fragilis* promotes naïve T cells to become Tregs that produce IL-10 and express high concentrations of CTLA-4; a person with cancer who has a microbiome with a high concentration of *B. fragilis* will not respond as well to the use of antibodies that block the function of CTLA-4 or may need a much higher dose of CTLA-4. Whereas *Bifidobacterium* species prime classical dendritic cells (cDCs) to increase cytotoxic T lymphocytes (CTLs), the cDCs then prime CTLs, providing the CTLs with better responses to cancer cells and enhancing the effect of anti-PD-1 cancer drugs [65]. How this developing information is utilized in prevention and treatment strategies remains a topic of considerable interest [66,67].

7. The microbiome and neurological disorders

It has long been recognized that a bidirectional interaction exists between the mammalian brain and the gut. With a better understanding of this process, the term 'brain-gut-microbiome' axis has been coined to characterize this relationship [68–70]. Within this axis, the microbiome can interact with the central nervous system by directly affecting neurotransmission via chemicals produced by gut microbes and indirectly by interactions with the endocrine and immune systems. Conversely, the autonomic nervous system, by effects on gut motility, intestinal secretions, and intestinal permeability, can change the composition and function of the gut microbiome [68,70]. Dysbiosis can thus result in disruption of this axis and, in this way, contribute to the pathogenesis of various neuropsychiatric disorders. There is strong evidence from animal studies and increasing evidence in human studies supporting this hypothesis [71,72].

Neurodegenerative conditions such as Alzheimer's and Parkinson's disease, commonly thought to be multifactorial in etiology, are influenced by the microbiome. These are some of the most debilitating conditions in medicine, with progressive loss of brain function and many overlapping clinical manifestations [73]. Alzheimer's and Parkinson's disease affect >30 million and 7 million people worldwide, respectively [74]. In both disease states, gastrointestinal symptoms are frequently observed, and there are evident disparities in structure and function of the gut microbiome of affected compared to unaffected individuals. Parkinson's and Alzheimer's patients have a less diverse microbiome than unaffected members of a control group [75]. Increased oxidative stress and inflammation likely lead to the accumulation of abnormal proteins in the brain [76]. With the prevalence of these diseases only rising as the aging population grows [77], along with limited efficacy and frequent undesired effects of current drug therapies, better modalities of treatment are needed.

Autism spectrum disorder (ASD) is a *neurodevelopmental* condition that is diagnosed in children with significant social and behavioral challenges and has a prevalence of >19% as of 2016 [78]. There is frequent concurrence with gastrointestinal symptoms [79]. In animal models as well as children and adolescents affected by ASD, there are differences in the microbiome compared to control subjects [71,76,80], suggesting that dysbiosis may be a contributor to the pathogenesis. The microbiota also appears to significantly influence brain development [81]. Probiotic treatments reduce the risk of ASD [82]. Attention deficit hyperactivity disorder(ADHD), another common neurodevelopmental condition affecting children and adults, has been looked at in a combined clinical cohort of both adolescents and adults in which those with ADHD were also seen to have altered microbiome composition [83].

Multiple sclerosis (MS), an *autoimmune* disorder affecting 2.5 million people worldwide, appears to have implicated in its pathophysiology, a disruption in the interplay between the gut microbiome and the immune system [71,76].

Furthermore, dysbiosis also appears to be a significant contributor to *neuropsychiatric* disorders such as anxiety disorders (a broader category that includes diseases such as generalized anxiety disorder, phobia(s),

PTSD, OCD(s)), and depression in animal and human studies. These diseases are common, with anxiety disorders estimated to have a prevalence of >20% of adults in the United States [84]. It is estimated that 31% or more of adults in the United States will experience some form of anxiety disorder at some point in their lives [85]. The microbiome of patients with bipolar disorder was shown to differ substantially from healthy controls [86]. At the same time, other studies suggest that probiotic and prebiotic treatments result in a significant reduction in depressive-like and anxiety-like behavior in rodents while effectively improving mood in humans [87,88].

In all of these neurologic or psychiatric conditions, current modalities of treatment leave much to be desired, with limited efficacy and frequent side effects due to lack of specificity. With an improved understanding of the microbiota-gut-brain axis in individual neurological and psychiatric diseases, the role of microbiota manipulation for treatment is being studied [71,89,90], including the role played by our diet [79,91]. While it is clear that the pathophysiology in these diseases is complex and multifactorial, and microbiome-based therapies are unlikely to be a panacea, they likely will add significantly to the armamentarium available for prevention and treatment.

8. The microbiome and metabolic syndrome

The term Metabolic syndrome (MetS), also called 'Syndrome X,' has various definitions, but it commonly refers to the presence of several risk factors for diabetes mellitus type 2, atherosclerotic heart disease, and strokes. The presence of MetS may also predispose one to non-alcoholic fatty liver disease, polycystic ovarian syndrome, certain cancers (such as esophageal, colon, gallbladder, and breast, among others), gallstone disease, and sleep apnea. According to the definition used by the National Institutes of Health, the presence of at least 3 of the following five risk factors is required to make the diagnosis: a large waistline, high triglyceride levels, a low high-density lipoprotein (HDL) level, high blood pressure, and high fasting blood sugar. The incidence of this condition is increasing, mirroring the increase in adult and childhood obesity worldwide [92,93].

Risk factors for the development of metabolic syndrome are genetic and environmental. The environmental and, therefore, modifiable risk factors include diet, physical activity and fitness, body weight, socioeconomic risk factors, and low birth weight. The role of diet has received much attention in the last two decades, and more recently, the potential role of the gut microbiota in MetS and its associated conditions, such as atherosclerotic disease and diabetes mellitus, has been a focus of interest. There are apparent differences in the gut microbiota in individuals with MetS, and consumption of the so-called 'Western diet' appears to contribute to this change [94,95]. It is proposed that this high-fat, low-fiber diet causes dysbiosis that alters intestinal permeability, resulting in translocation of microbial components and products of metabolism. These result in chronic liver and adipose tissue inflammation, leading to the mentioned manifestations of MetS [95,96]. The microbiota can modulate glucose and lipid homeostasis and regulate satiety and energy production [96].

Even though the field of study of the microbiota is still in its infancy, it is clear that diet has a significant influence on the composition and function of the gut microflora in the host, and many of the known benefits of dietary change are very likely mediated by this mutually beneficial interaction [95].

9. The microbiome and diet

Globally, life expectancy continues to steadily increase, with some slowing and stagnation recently due to socioeconomic factors, drug-related mortality, and events such as the COVID-19 pandemic [97–100]. With an increased life expectancy, the number of healthy years lost to disability has also increased [101], with implications for primary and secondary preventative care planning and healthcare

budget allocation. Despite the mild aberration caused by the COVID-19 pandemic, life expectancy in the USA and globally has gradually increased. Furthermore, the global trend of decreasing total fertility rates (the average number of children a woman would bear if she survived through the end of the reproductive age span [102]) clearly indicates that the population in many countries is aging. Therefore, from a quality of life and economic perspective, efforts that promote a longer, disease-free life should be vigorously pursued.

Consensus accepts that diet is an essential factor in both primary and secondary prevention of non-communicable chronic diseases such as atherosclerotic disease [103,104], type 2 diabetes mellitus, and obesity, to name a few.

Recently, there has been increased interest in 'Longevity Blue Zones,' described as geographic areas where inhabitants experience longer lives with relatively few age-related disabilities. These areas include Loma Linda, California; Okinawa, Japan; Sardinia, Italy; Nicoya, Costa Rica; and Icaria, Greece. While the reasons for this longevity are poorly understood, there is some indication that diet may play a role [105–107], among other factors such as a high level of family solidarity, social interaction, and physical activity [108].

Results from the Nurses' Health Study cohort observed a 17% reduction in total mortality, 17% lower risk of total mortality, 28% lower risk of cardiovascular disease (CVD) related mortality, and 30% lower mortality from non-CVD, noncancer causes of mortality in subjects who consumed a diet rich in vegetables, fruit, legumes, fish, poultry, and whole grains compared to subjects consuming diets rich in red meat, processed meat, refined grains, French fries, sweets, and desserts [109].

The Mediterranean diet (MeDiet) has also received attention for its protective effect on chronic non-communicable diseases. The diet emphasizes an abundance of vegetables and fresh fruit, olive oil as the principal fat source, consumption of moderate quantities of fish, poultry, and wine, limited dairy products, and reduced amounts of red meat [110]. The MeDiet has particular benefits in the primary and secondary prevention of cardiovascular disease, and this is well established [103,110], with improvements in inflammatory, lipid, and glycemic profiles in subjects with atherosclerotic disease. The MeDiet is comparable in its effects to other treatment interventions, including aspirin, various antihypertensive medications, HMG Coenzyme A inhibitors, and physical activity [110]. Research findings suggest that the MeDiet confers protection from the development of metabolic syndrome and has been shown to reverse the components of metabolic syndrome [111,112]. Adherence to MeDiet significantly helps prevent and manage diabetes mellitus [113,114]. It may be protective against the development of colorectal cancer and possibly other cancers [115].

Common to these beneficial diets is the increased content of plant-based foods. As indicated, the institution of plant-based diets improves inflammatory markers and positively changes metabolic and lipid profiles. As a result of our expanding understanding of the gut microbiota, mechanistic connections between diet, gut-microbial community structure/function, and human health are coming into focus. Traditional methods of studying gut microorganisms, mainly bacteria, typically involved isolation and culture in external media, elucidating individual characteristics of cell biology, biochemistry, physiology, ecology, evolution, and clinical aspects. However, recent techniques, including next-generation DNA sequencing technologies, including shotgun metagenomics, allow for studying the entire genome of all organisms present in a sample from a specific location. The presence of individual microorganisms can be determined by matching the 16S ribosomal RNA contained in the sample with known libraries of bacteria cataloged in this way. Studying the entire genome also allows evaluation of the metabolic potential of the organisms in the sample, with consideration even to bacteria not yet isolated or classified by 16S ribosomal RNA gene identity. Moreover, these methods are helping us recognize that communities of organisms lead to phenotypical changes of the microbial members in ways that influence heath and disease.

Transcriptomics evaluates messenger RNA (mRNA) contained in a sample, thereby providing insight into gene activity; combined with proteomics and metabolomics (the study of the protein products of mRNA and the metabolites produced by them, respectively), these multi-omic technologies can lead to the elucidation of metabolic pathways present in a microbial community. Our current understanding of the gut microbiome suggests that extensive cooperation and coordination occur between different bacterial species in a microbial community, and allow for greater comprehension of the complex interplay between the host and gut microbiota.

Dysbiosis, a perturbation of a microbial community's balanced, homeostatic state, allows for the induction and subsequent perpetuation of certain disease states. The concept of what might be a 'healthy microbiota' is thus essential to understand and has been, and continues to be, the subject of numerous studies. A detectable departure from a healthy state can aid in diagnosing these disorders, and manipulations aimed at correcting these imbalances may lead to developing strategies for prevention and therapy. Most studies to date have focused on the composition of the gut microbiota community. Findings suggest significant variations in gut microbiota community structure in healthy subjects, with diet, geography, and socioeconomic factors, among others, having an impact [116,117]. Due to significant variation, observed taxonomic composition alone is not a viable method to characterize a healthy microbiome [116]. Even though microbial composition may vary, from a functional standpoint, healthy microbiomes may be comparable [118]. Metagenomic studies have allowed us to evaluate the functional characteristics of the microbiota, and the available evidence suggests that this is a significant determinant of microbiota health in this nascent field of study [118]. The capacity of the gut microbiota to withstand change caused by environmental pressures, such as the use of antibiotics and alterations in diet, is considered an essential feature of a healthy microbiota. In comparisons of the microbiota in health and disease, a highly diverse microbiota has been associated with health and stability over time [118,119]. Logically, this may be related to the functional redundancy that results from having a more diverse set of microbes [116].

The importance of the gut microbiota in the pathogenesis of non-communicable chronic diseases (NCDs) is, therefore, without question, even if the details are still being elucidated. The link between gut-microbiota dysbiosis and NCDs has led to an interest in modalities to alter the microbiota in beneficial ways as a form of treatment. The effect of diet on the microbiota is well established, and even acute changes in diet can lead to rapid (within 24 h) changes in microbial composition that can quickly revert with the resumption of baseline diet [120]. Diet appears to play the most crucial role in the long-term maintenance of the microbiota compared to other modalities such as prebiotics, probiotics, and antibiotics [117,121].

The Western diet is rich in animal protein, high in fat, and low in plant-based fiber. In contrast, diets such as the Mediterranean diet have a fatty acid profile rich in both monounsaturated and polyunsaturated fatty acids, higher levels of polyphenols and other antioxidants, high intake of plant-based fiber and other low glycemic carbohydrates, and relatively greater vegetable than animal protein [122–124]. These latter diet types and their effect on the gut microbiota appear beneficial in preventing and managing NCDs [122,125–127]. Recent research suggests adding fermented foods may provide additional benefits [128,129].

10. Soil microbiome and plant microbiome

Like animals, plants have evolved to coexist with microorganisms. In specific examples, adaptations to environmental conditions allowed a species to survive due to symbiosis. For example, eukaryotic cells of plants and animals contain organelles derived from Proteobacteria ancestors (i.e., endosymbiotic theory). In plants, this symbiotic relationship is evident in chloroplasts, which contain chlorophyll and utilize the energy from sunlight to synthesize carbohydrates. Plants have diverse microbial communities encompassing the endosphere (plant interior), phyllosphere (aerial environment), and rhizosphere (zone of soil immediately adjacent to the roots [130,131]). Specifically, the rhizosphere, which contains the majority of the plant microbiota, has a combined genome much larger than the plant and serves a similar function as the microbiota contained in the human gut [131].

There are many functional similarities in the relationships between plants and animals and their respective microbiotas, including the importance of nutrient uptake, prevention of colonization by pathogens, and modulation of host immunity [131]. The health and productivity of plants and their ability to withstand stress are influenced by the diversity of their surrounding microbial community. Over the last several decades, metagenomic studies and 16s ribosomal RNA have helped characterize the community structure of the plant microbiota and gain an understanding of functional aspects [132].

11. Making the case for regenerative agriculture over Conventional/Industrial Agriculture

11.1. Regenerative Agriculture (RA) versus Conventional/Industrial Agriculture (IA)

In this discussion, Conventional/Industrial Agriculture (IA), also called industrial farming, refers to farming methods developed in the late 19th and early 20th Century and have been used widely, especially in industrialized countries, since World War 2. IA is responsible for the so-called 'Green Revolution,' which dramatically increased the availability of food grains (especially wheat and rice) in the late 20th century. These systems of farming include the use of synthetic fertilizers, pesticides, herbicides, intensive irrigation, genetically modified disease-resistant, and high-yielding plants and animals, large-scale monocropping, intensive tillage of the land with decreased or absent fallow periods, and high stocking density in animal husbandry with associated concentrated animal feeding [133]. Energy derived from fossil fuel is used to produce ammonia-based fertilizer and other chemicals and to power the heavy machinery used in industrial agriculture. These practices contribute significantly to greenhouse gas emissions [133,134].

IA leaves much to be desired regarding factors contributing to human health, a few examples of which are explained here. In terms of soil quality, it has been found that conventional farming (i.e., overgrazing, overuse of water, overcultivation) has led to unsustainable rates of soil erosion and harms soil-benefitting organisms due to overgrazing, overuse of water, and overcultivation practices [135,136]. With regards to food quality, while increasing crop production during the Green Revolution through the development of high-yield plant varieties [137], IA has led to many consumers experiencing seemingly paradoxical nutritional deficiencies (ex., vitamin A, zinc) in the human population due to nutritional deficiencies in crops [135]. The use of chemicals such as the herbicide glyphosate is widespread. In theory, glyphosate is considered safe because it inhibits an enzyme found in plants and not in animals [138]; however, the enzyme in question, 5-enolpyruvylshikimate-3-phosphate synthase, is present in some microorganisms, and can thus affect the balance of the microbiota, resulting is dysbiosis and risk for disease in both plants and the animals exposed to crops treated with this herbicide [139]. A recent review summarized the effect of glyphosate and several pesticides, insecticides, and fungicides on the microbiota, primarily in animal studies [140]. This data suggests pathogenetic links to human diseases associated with these chemicals, but further studies are necessary to elucidate fully. Additionally, pesticides are associated with increased risk for cancer as well as reproductive and endocrine dysfunction [136].

Apart from the effects of IA on soil and food quality, the impact of IA on other important factors contributing to human health – namely, ecosystem and climate health – is worrisome. For one, pesticides pollute surface waters and groundwater and harm honeybees (which pollinate a

considerable share of crops in the US) [141]. Moreover, 20% of human-generated greenhouse gasses derive from conventional farming practices [136]. Likewise, one would expect these chemicals to affect both the soil and plant microbiota, with consequences for soil and plant health and the quality of food produced from these sources. Preliminary work confirms this is indeed the case [142], but as with human diseases, much work remains to be done to fully understand these interactions.

The use of antibiotics in industrial food animal production has long been recognized as a significant contributor to antimicrobial resistance and its spread. The use of subtherapeutic doses of antibiotics in animal husbandry can lead to the development of resistance, and these resistant strains can be transmitted to humans directly from the environment or by consumption of animal products containing these organisms [143].

While many other adverse effects of IA exist, this section will focus primarily on the benefits that an alternative to IA, regenerative agriculture, may be able to provide. The term Regenerative Agriculture (RA) is best used to refer to an agro-ecological approach to farming that seeks to address the problems of IA and could lead to a more sustainable food system. The health of the soil is a major priority [144]. It is seen as distinct, although incorporating principles from organic farming, low-input farming, free-ranging animal husbandry, and biodynamic farming, among others [135]. All of these approaches to farming seek to simulate processes that occur in nature that foster increased biodiversity and minimize the destruction of the environment. From an agronomic perspective, the philosophy of RA includes producing nutritious food at a high yield that is free of biocides. Over time, RA practices improve soil fertility and productivity. Infrequent or no tilling and use of cover crops are integral practices. There is increased water percolation and retention and safe water runoff. RA avoids using biocides that utilize biological interactions to prevent pest and weed impacts. Nutrient flows within farming systems integrate the soil fauna and flora, including the microbiota, resulting in less environmental destruction. Improved carbon sequestration results from RA practices. The use of biological nitrogen fixation is favored over using ammonia-based fertilizers. Animals are fed and kept in a manner that precludes the use of antibiotics and hormones to prevent them from getting into food derived from these sources. Where practical, crops and animal rearing are combined. RA practices also consider the social and economic conditions of the farming personnel and aim to optimize these as well. While national and state-level planning will be necessary to fully incorporate RA practices into food systems, because of the closed loops involved in nutrient and water cycling, a high degree of local and regional self-reliance is necessary because of the closed loops involved in nutrient and water cycling [135,144–150].

11.2. Effects of soil health on crop health/food quality

Given the potential of soil health to improve crop quality, it is crucial to consider the impacts of RA practices on the soil environment and possible linkages to advance food quality. There is a need to conduct multiple season side-by-side studies comparing the food quality of IA and RA crops due to the numerous confounding factors controlling crop quality (such as cultivar variety, environmental conditions, and farm management). While more studies are needed to assess the role of soil health on crop health and, ultimately, human health, preliminary studies have found notable results. Giller et al. summarized findings from multiple groups demonstrating the impacts of each principle of RA and its associated practices on soil health and biodiversity [151]. RA practices (e.g., minimizing tillage and maintaining crop cover) improved soil health, potentially contributing to enhanced biodiversity [145].

Food quality and nutrient density measurements comparing food produced in IA settings versus farms utilizing RA principles have provided conflicting results, with challenges related to scientific/statistical methodology, differing farming practices, and confounding related to industry-sponsored studies, among other sources of bias. One of the earliest studies suggested composted manure resulted in much lower nitrate levels (less risk of carcinogenicity) in leafy vegetables compared to nitrate-based inorganic fertilizer [152]. Similar findings were seen with other vegetables, with higher vitamin C and trace elements and less incidence of biocide residues [153]. Meta-analyses comparing conventional and organic fruits and vegetables observed improved vitamin C, iron, magnesium, and phosphorus and significantly fewer nitrates and lower amounts of some heavy metals in organic crops [154]. A follow-up meta-analysis observed consistently higher mineral content in organic produce [155], and an additional meta-analysis concluded organic crops have higher concentrations of antioxidants, lower concentrations of cadmium (a toxic heavy metal), and a reduced frequency of pesticide residues than the non-organic comparisons across regions and production seasons [156]. The most recent meta-analysis also found that crops from organic systems have elevated concentrations of several groups of beneficial nutrients, including secondary metabolites with antioxidant activity, carotenoids, vitamins, total flavonoids, and phenolic acids, than those managed conventionally [157]. These latter few studies highlight the importance of phytochemicals in assessing food quality, as their importance in human health is increasingly being recognized, and their quantitation is critical in any meaningful comparisons.

A common theme of previous research suggests that our current understanding of factors influencing food quality and its role in health and disease has extensive limits. For example, the concept of dark matter/nutrients such as plant-derived amino acids and their influence on human protein structure and subsequent effects on immune function, specific food-derived pathological misfolded prion proteins and their impact on nervous-system function, and microRNAs from plant foods and their influence on the genetic expression of both enteric bacteria and potentially endogenous cellular function [158]. Recent studies comparing IA and RA show promise for increasing food quality and nutrient density. Montgomery et al. observed that regenerative practices consistently improved the nutrient profile of crops compared to those produced via conventional methods by increasing the quantity of soil organic matter and that of various vitamins, minerals, and phytochemicals [159]. Additionally, diversification in Midwest crop rotations increased crop yields and nutritional quality of crops, and altered cation exchange capacity, salt-extractable soil carbon, and microbial biomass without sacrificing profitability [160]. The soil-building principles initiated by RA practices will foster greater soil microbiota diversity, thus increasing diversity within the plant microbiota. Theoretically, this should provide greater crop nutrient quality, presumably leading to improved food products (Fig. 3). These studies offer insight into the possibility that RA may improve food quality, lessening the impact of various (chronic) diseases that arise due to lack of proper access to food with increased nutrient quality.

11.3. Animal microbiome and animal source foods (ASF)

It is well established that the consumption of animal products can influence the human gut microbiota and thus overall health [161]. In parallel to the work being done looking at the role of the human gut microbiome in states of health and disease, there is increasing interest in studying animal microbiomes for the same reasons. Expectedly, the gut microbiomes of livestock used as ASF is receiving attention, as this appears to affect the quality of meat produced by influencing fatty acid composition and oxidative stress in adipose and muscle tissue [162–164]. A better understanding of the relationship between animal microbiomes and health/ASF quality may lead to less use of additives such as hormones and antibiotics and the ensuing downstream effect on human health [164,165]. Comparative studies looking at ASF derived from RA practices have shown improved fatty acid (FA) profiles, but other important parameters such as minerals, antioxidants and individual FAs are less well studied thus far [166], indicating a gap to be filled by future research. Studies comparing the effect on the human gut microbiome of ASF produced by RA methods compared with IA methods

are also lacking.

11.4. More than food: additional ecosystem benefits of regenerative agriculture

The potential benefits of utilizing RA practices are extensive, offering tangible solutions to human health and nutrition and resiliency to the global climate crisis [167]. Using organic amendments (i.e., compost and manure) in combination with biological nitrogen fixation in place of chemical fertilizer establishes long-term soil fertility. Through efficient use of resources, RA ensures minimal waste and limits the emission of greenhouse gases [168]. Soil structure is actively improved in RA-managed systems as micro- and macro-organism diversity is increased with the additional benefit of producing high-quality, nutritious food with minimal environmental impact [169,170]. Maintaining continuous ground cover on soil limits water and wind erosion, providing an additional example of RA's capacity to maintain and recycle resources while providing a higher degree of environmental sustainability. On a systems level, RA can potentially improve long-term financial profitability as fewer resources are required for crop production, and typically, crops are purchased at a higher price [145].

Local and state legislators can add to the financial benefits by implementing legislation encouraging environmentally friendly and sustainable farming practices [171]. A recent and impactful example of this is the Soil Quality Act of 2019, which provided farmers with financial incentives to use renewable sources, increase crop nutrient quality, and actively increase the biodiversity of their soil microbiome. Therefore, RA is a unique strategy that can improve human, soil, and environmental health while providing financial benefits (Fig. 2).

12. Conclusion

Our understanding of the role of microorganisms has evolved significantly since Robert Hooke and Antoni Van Leeuwenhoek first described microscopic organisms in the latter half of the 16th Century. During the late 1800s and early 1900s, microorganisms were largely considered agents of disease, most notably through the work of Robert Koch, who first described the causative agents for tuberculosis (*Mycobacterium tuberculosis*) and anthrax (*Bacillus anthracis*), ushering in the burgeoning field of bacteriology, and Heinrich Anton de Bary, founder of Plant Pathology and modern mycology. However, Sergei Winogradsky's pioneering work demonstrated the importance of microorganisms in biogeochemical cycling, specifically of nitrogen, iron, and manganese. For this work, he is often considered the father of microbial ecology. The science of microbial ecology took a significant step forward through the work of Kary Mullis, who invented the polymerase chain reaction (PCR), and Carl Woese, who developed the application of 16S Ribosomal RNA gene comparisons to characterize the phylogeny of the microbial world. The study of metagenomics and its associated -omics has catapulted the study of microbiomes into the modern era. Through these discoveries, we better understand the role of microorganisms in maintaining human health, the causation of various non-infectious diseases, their potential to support and improve soil and plant health, and the health of animals used for food.

From an evolutionary perspective, prokaryotes (bacteria and archaea) were the first organisms rooting the aboriginal branch of the eukaryotic tree of life [172]. The First Common Eukaryotic Ancestor (FCEA) arose from the Asgard superphylum of Archaea. However, specific evolutionary transitional steps from prokaryotes to FECA remains a topic of significant research interest [173]. Since eukaryotes evolved in the presence of prokaryotes, it stands to reason that prokaryotes have shaped the trajectory of macro-organism evolution. Case in point, the
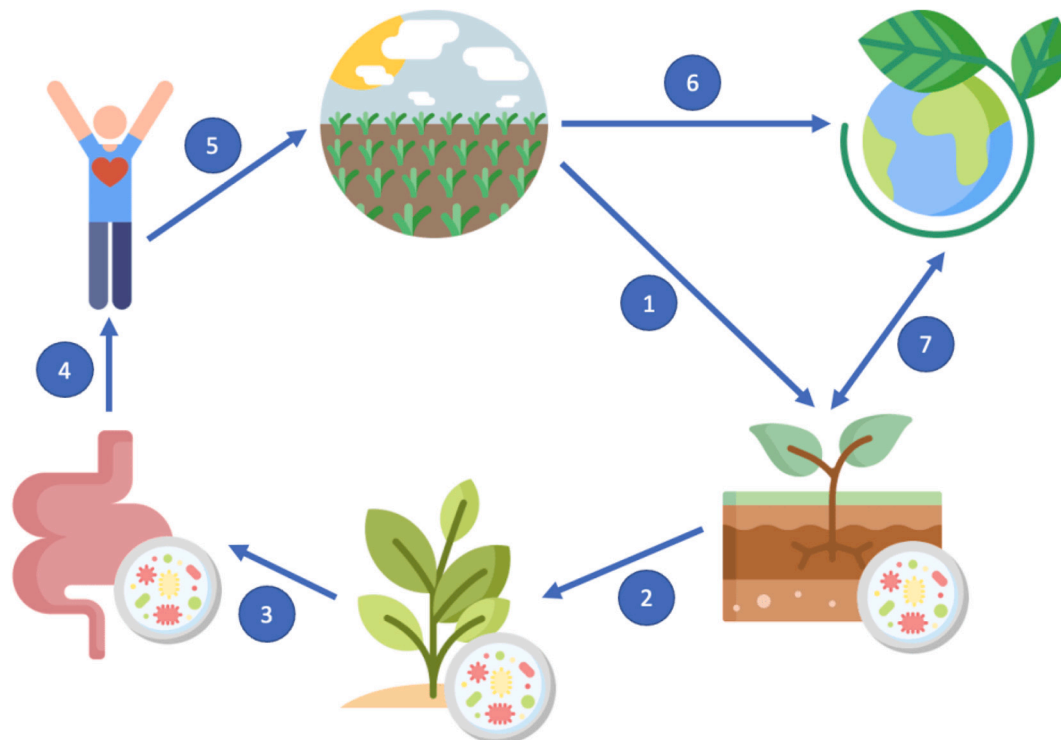

Fig. 2. The relationships between the above factors are more complex, and their detailed interactions include features beyond current knowledge; however, a humble effort has been made to illustrate the key connections we are currently aware of based on findings from the last several decades of research. 1) Regenerative agriculture leads to healthy soil and soil microbiomes 2) Healthy soil and soil microbiomes lead to healthy plants and plant microbiomes 3) Healthy plant and plant microbiomes lead to healthy human gut microbiomes 4) Healthy human gut microbiomes lead to overall human health 5) Healthy humans can continue to practice regenerative agriculture 6) Regenerative agricultural practices also contributes to planetary health 7) A healthy planet contributes to healthy soils, and vice versa.
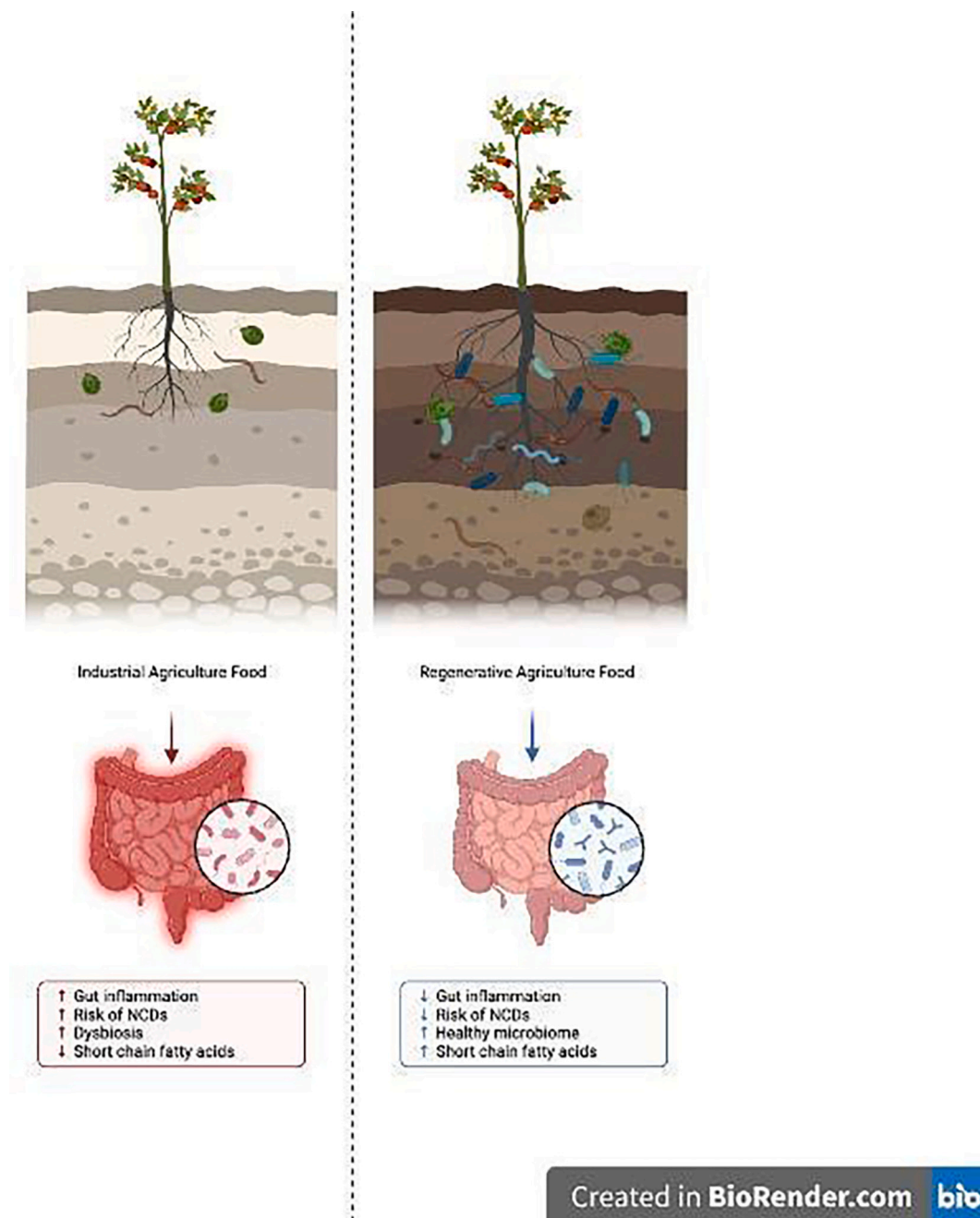
Fig. 3. The outward appearance of fruit may not provide a clear indication of the underlying agricultural practices used to grow them. However, the stark differences in soil quality between Industrial Agriculture (IA), left, and Regenerative Agriculture (RA), right, are likely to impact the health of the end consumer, especially regarding the gut microbiome. This figure highlights how RA practices prioritize restoring and maintaining soil health, resulting in improved plant health and food quality and ultimately leading to a healthier gut microbiome in humans. In contrast, IA practices, often relying on synthetic inputs, can harm the soil microbiome and may negatively affect human gut health.

hologenome theory of evolution (HTE) suggests that symbiotic interactions between microorganisms and their macro-organism hosts (termed the holobiont) facilitated greater fitness to environmental stressors, playing a critical role in adaptation as well as the evolution of higher organisms [174]. Counter to HTE, Stencel, and Salamon [175] argue that symbiotic interactions between macro-organisms and their microbiota represent units of co-operation potentially facilitating greater macro-organism fitness rather than traits subject to selection.

Nonetheless, studies indicate the importance of micro- and macro-organism symbiosis in digestive processes [176] and in the development of the host immune response [177]. Considering this, the findings summarized in this review are therefore not surprising. Disruptions in the host-microbiota relationship caused by dysbiosis can play a significant role in the pathogenesis of human disease. Possible manipulations of host microbiota provide opportunities for novel treatments and prevention strategies. However, specific studies are limited, suggesting more animal and human trials are needed.

Various methodologies have been employed to alter patient gut microbiota, including pre-and pro-biotics, antibiotics, and fecal transplant modalities; however, the simplest and most effective approach appears to be dietary manipulation. The healthy diet described herein as primarily plant-based, incorporating whole grains, fruits, vegetables, legumes, minimal red meat, and processed foods, appears ideal. The addition of fermented foods potentially provides added benefits.
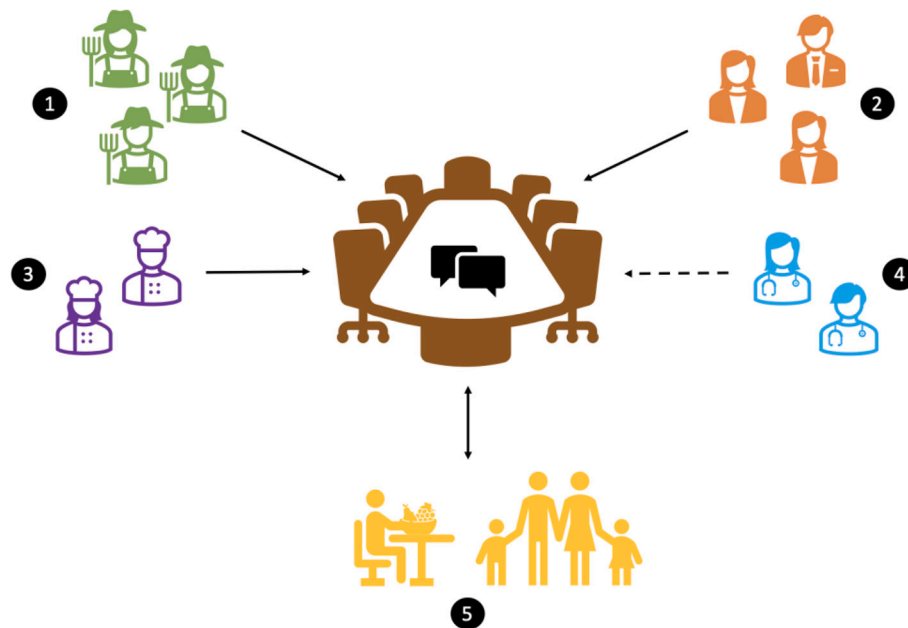
Fig. 4. Many groups participate in discussions regarding agricultural practices, from farmers (1), food processing, transportation, distribution, and retailing experts (2), chefs (3), and end consumers (5). The voice currently missing from the roundtable discussions is that of the healthcare community (4), whose input will be critical to achieving system-wide change.

Considering the importance of diet on the gut microbiome's structure and function, factors influencing crop nutrient quality (i.e., farming practice, cultivar selection, and harvest/storage practices) have received limited attention. Regarding environmental and management factors, future research should consider crop accumulation of phytochemicals (i. e., minerals, vitamins, phytosterols, and antioxidants). Specifically, the influence of food production practices and effects on the gut microbiome should be considered.

Like dietary effects on the human gut microbiome and its critical influence on human health, a similar analogy can be applied to soil health and its effect on the plant microbiome. For example, the structure and functional redundancy of the rhizosphere microbial communities can influence overall plant health and the nutritional quality of the crops produced. RA practices improve the structural complexity and functional redundancy of the rhizosphere microbial community through management practices, and preliminary research suggests that crops derived from RA practices maintain greater nutrient quality than those produced utilizing industrial practices. Furthermore, crops produced and animals reared utilizing RA are devoid of biocides, hormones, and antibiotic residues typically identified in industrially produced crops/ ASF. A recent study observed significantly greater concentrations of *Per*- and polyfluoroalkyl substances (PFAS) in fresh and frozen vegetables produced by industrial practices compared to organic/regenerative methods [178].

Lastly, the planetary benefits regarding greater carbon sequestration, soil nutrient retention, and improved water quality derived from RA practices cannot be ignored. Mitigating significant factors driving global climate change provides direct and indirect benefits to the health of our patients. Implementing increased production of RA crops is not straightforward, requiring, first and foremost, increased demand, changes in priorities, ideology, and traditions from the standpoint of farmers, educational initiatives, financial support, and the support of global, national, and regional programs. When human health becomes the focus, the impetus to increase acreage dedicated to RA will increase, leading to wider availability and reduction in food cost, especially of crops produced regionally (close to where people live), is likely to follow (Fig. 4).

The last 20 years of research regarding the importance of both animal and plant microbiomes to human health has identified numerous vital connections. However, the complete picture has yet to come into focus. There is increasing evidence that the microbiomes of humans, plants, and the soil are all interrelated, and the soil is the ultimate repository of multitudes of important organisms that have been present for time immemorial. Treating them with the respect they deserve will allow us to reap benefits from many fronts.

Future directions

· More animal and human studies investigating the relationship between the gut microbiota and various human diseases and the effect of food on primary and secondary prevention.
· Similar studies involving soil and plant microbiotas would also be instructive.
· Continued exploration of microbiota manipulation in preventing and treating human diseases. In the botanical world, soil and plant microbiota manipulation for improved plant health and, thus, food quality.
· Reassessing how we look at food quality and its nutritional content while considering emerging information regarding essential entities such as phytosterols and other dark nutrients.
· Continued study of the effect of agricultural practices on food quality and other potential benefits including, but not limited to, carbon and water cycling, pollution, effects on habitat biodiversity, and climate change.

CRediT authorship contribution statement

Davendra Ramkumar: Conceptualization, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Aileen Marty:** Writing – original draft, Writing – review & editing. **Japhia Ramkumar:** Visualization, Writing – review & editing, Supervision, Conceptualization. **Holly Rosencranz:** Writing – review & editing. **Radhika Vedantham:** Visualization, Writing – original draft. **Modan Goldman:** Visualization, Writing – original draft. **Erin Meyer:** Conceptualization, Funding acquisition, Writing – review & editing. **Jasia Steinmetz:** Writing – review & editing. **Amy Weckle:** Writing – review & editing. **Kelly Bloedorn:** Visualization, Writing – review & editing. **Carl Rosier:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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