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Environmental Influences on the Human Microbiome and Implications for Noncommunicable Disease

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Abstract

The human microbiome contributes metabolic functions, protects against pathogens, educates the immune system, and through these basic functions, directly or indirectly, affects most of our physiologic functions. Here, we consider the human microbiome and its relationship to several major noncommunicable human conditions, including orodigestive tract cancers, neurologic diseases, diabetes, and obesity. We also highlight the scope of contextual macroenvironmental factors (toxicological and chemical environment, built environment, and socioeconomic environment) and individual microenvironmental factors (smoking, alcohol, and diet) that may push the microbiota toward less healthy or more healthy conditions, influencing the development of these diseases. Last, we highlight current uncertainties and challenges in the study of environmental influences on the human microbiome and implications for understanding noncommunicable disease, suggesting a research agenda to strengthen the scientific evidence base.

1. INTRODUCTION

Substantial advances have accumulated in the past 10 years in understanding the role of the human microbiome in health and disease; this progress has been based largely on the transition from classic microbial culture-based assays to the use of high-throughput comprehensive microbiome characterization through targeted bacterial 16S rRNA (ribosomal RNA) sequencing, whole-genome shotgun sequencing, and, more recently, microbial transcriptomics and metabolomics. The National Institutes of Health (NIH) Human Microbiome Project (47) and other international initiatives (40, 75) have provided resources, methods, and discoveries that link interactions between humans and their microbiomes to health-related outcomes (47, 74). These advances have also been greatly supported by the development of expanded microbial taxonomic databases, analytic bioinformatics pipelines, and novel statistical approaches for study of the microbiome's relationship to health and disease. Decreasing sequencing cost and rapidly expanding sequencing technology further facilitated the development of relatively large-scale human and experimental studies, providing complementary insight on microbial determinants of disease in human populations and on the underlying mechanistic basis of disease. Human studies have been strengthened by the increased attention to microbiome-related sample collections in diverse populations, and experimental studies have advanced through the development of experimental animal models, including germ-free humanized mouse models.

Research is also advancing our understanding of the environment as a major driver of variability in the human microbiome. Evidence from 2018 shows in families that genetic ancestry or individual polymorphic variants have a minor role in gut microbiome composition (<2%), whereas over 20% of the variance in microbiome diversity can be inferred from shared environmental factors, such as those associated with diet and lifestyle (95). In this article, we first review research on the human microbiome and its relationship to several (classically considered) noncommunicable human conditions, including orodigestive tract cancers, neurologic diseases, diabetes, and obesity. Then, we highlight the scope of known and suspected environmental factors that may push the microbiota toward less healthy or more healthy conditions, influencing the development of these diseases. We consider the environment in the broad sense, involving the contextual social and built environment and environmental toxicants, and with respect to individual behaviors, including smoking, alcohol, and dietary intake (see **Figure 1**). Last, we highlight current uncertainties and challenges in the study of environmental influences on the human microbiome and implications for understanding the microbial basis of noncommunicable disease, suggesting a research agenda to strengthen the scientific evidence base.

2. THE HUMAN MICROBIOME AND ITS INTERINDIVIDUAL VARIABILITY

The human microbiome is composed of bacteria, archaea, viruses, and eukaryotic fungal microbes that reside in and on our bodies. These microbial cells that colonize the human body, including the mouth and gut, are at least as abundant as our somatic cells and certainly contain far more genes than our human genome. An estimated 500–1,000 species of microbiota exist in the human body at any one time (127), although the number of unique genotypes could be orders of magnitude greater than this estimate (61). Each bacterial strain has a genome containing hundreds of genes, offering substantially more genetic diversity and hence flexibility than the human genome. These microbes and their microbial molecular functions have tremendous potential to impact our physiology, both in health and in disease (45).

The human microbiome, to maintain symbiotic relationships within the body, contributes metabolic functions, protects against pathogens, and trains and develops the immune system, and,

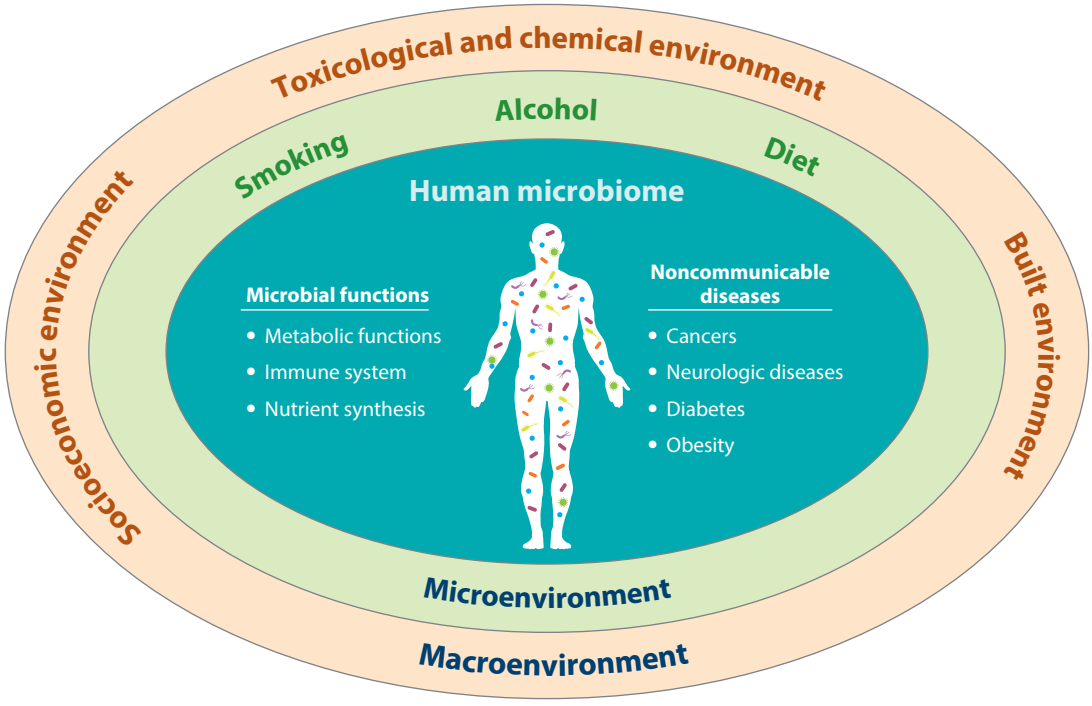

Figure 1

The effect of the environment on human health is a complex set of interactions between multiple exposures that, alone or more commonly interdependently, affect various structures and functions of the microbiome. This figure illustrates how environmental exposures have a direct impact on the human microbiome, implicated in human health and diseases, including orodigestive tract cancers, neurologic diseases, diabetes, and obesity. These environmental exposures are influenced by and interrelated with the macroenvironment, including the toxicological and chemical environment, built environment, and social environment, as well as the microenvironment, including smoking, alcohol, and dietary factors. Although external environmental impacts are illustrated, individual factors, such as age, sex, and genes, also interact with and eventually determine exposure, dose, and any subsequent response and effect.

through these basic functions, directly or indirectly affects most of our physiologic functions. People tend to possess a core microbiome, sharing common microbiome members of microbial species (45). However, different people harbor very different collections of microbes with substantially varying densities even among conserved taxa. This significant interindividual variability between persons is a potential source for differential susceptibility to disease.

3. THE MICROBIOME IMPLICATION FOR NONCOMMUNICABLE DISEASES

3.1. Orodigestive Tract Cancers

Microbes induce at least 60% of human orodigestive tract cancers (81), suggesting the tremendous potential of controlling microbe-related processes for orodigestive tract cancer prevention and treatment (13). Epidemiological studies consistently report the association between oral diseases and risk of orodigestive tract cancers, including cancers of the head and neck, esophagus, stomach, and pancreas. Because oral diseases have an important microbiologic basis, these observations have led to the hypothesis that the oral microbiome is related to the development of orodigestive cancer (4). Case-control studies nested within large population-based cohort studies found that the

prediagnostic oral microbiome, assessed using mouth wash samples, is associated with subsequent development of orodigestive tract cancers of the head and neck (3, 43), esophagus (87) and pancreas (34). Several studies have also pointed specifically to a link between gut microbiome *Fusobacterium* and other species and colon cancer (5, 54, 116) and between the gut microbiome and inflammatory bowel disease (47) and colorectal adenoma (85).

Microbial-derived signals modulate numerous hallmarks of cancer through diverse mechanisms. In general, bacteria cannot directly induce cancer; the process is commonly accompanied by chronic inflammation and requires independent mutations in oncogenic signaling pathways (131). Studies further indicate (9, 89) that the cross talk between the microbiome and the host is critical to orodigestive tract oncogenesis by regulating innate and adaptive immune function in the tumor microenvironment (27). A bacteria–cancer model proposes that gram-negative bacteria promote carcinogenesis, as the lipopolysaccharide bacterial outer membrane provides the immunogenic stimulus for innate immune system response via Toll-like pattern recognition receptors, leading to genetic mutations caused by nuclear transcription factor NF-κB protumorigenic cytokine release, immune cell recruitment, and reactive oxygen release (131). Thus, a microbial role in shaping of the tumor immune microenvironment is of great potential importance in the pathogenesis of cancer, particularly of the orodigestive tract.

3.2. Neurologic Diseases

The gut and the central nervous system interact through the gut–brain axis, modulating central nervous system function, including affective-like behavior, cognitive performance, fatigue, and sleep. Research indicates that the gut microbiome, through influence on this gut–brain axis, may play a role in certain neuropsychiatric and neurodevelopmental disorders (37, 97), altering behavior and potentially affecting the onset and/or severity of nervous system disorders. Germ-free mice and mice treated with antibiotics display a host of neuroimmune dysfunction and behavioral deficits (37). The gut microbiome has been linked, largely in preclinical models, to disorders of the brain, including anxiety, depression, and epilepsy, as well as autism spectrum disorder (104). In humans, evidence for interplay between gastrointestinal pathology and neuropsychiatric conditions has been reported in conditions such as anxiety, depression, and autism (124); however, causality remains unproven. Uncovering mechanisms that are utilized by the microbiome to mediate gut–brain connections may provide novel opportunities to target therapies to the gut in order to prevent and treat neurologic disorders.

3.3. Diabetes

A substantial body of literature has provided evidence for the role of gut microbiota in the etiology of prediabetes and type 2 diabetes (47). A 2020 review (39) summarized more than 40 published human studies. For example, in prediabetics, Zhou et al. (143) showed that molecular signatures based on the gut microbiome and inflammation and immune markers predicted for the onset of type 2 diabetes. Two seminal studies (51, 90) reported that gut microbiome profiles differ between type 2 diabetes patients and nondiabetic controls. A subsequent study (138) showed that gut microbiota in type 2 diabetic patients mediates the therapeutic effects of metformin, which is used for diabetes control. Zeevi et al. (142) developed personalized diets for optimizing blood glucose level in type 2 diabetes patients, with consideration for personalized dietary habits, physical activity, and gut microbiota. The researchers then showed in a blinded randomized controlled dietary intervention trial that application of this algorithm led to improved postprandial glucose responses. The current challenge is to replicate the precise components of the gut microbiome (39), which drive this heterogeneous, multifactorial, multiorgan disease.

3.4. Obesity

The prevalence of obesity has increased on a global scale over the past several decades, leading to premature death (2, 12) and many noncommunicable diseases (134). Although the fundamental cause of obesity is an imbalance between energy intake and expenditure related to physical activity linked to work and home environments, gut microbial composition (57) is a well-established factor for weight gain, along with other mechanisms, such as genetic variation (62) and epigenetic regulation (133). Experiments in germ-free mice colonized with gut microbiota transferred from wild-type mice (10), obese mice (128), or obese humans (92) have demonstrated that the microbiome plays a critical role in weight gain and adiposity in this test system, implicating gut microbes in the establishment of the obese phenotype. These experimental findings lead to the question of whether the microbial composition of the gut confers susceptibility to weight gain in humans, whether genetically determined (58) or diet induced (44, 70, 125). An early report in a small sample of humans (59) was consistent with findings in mice that the obese state is associated with an increase in the relative abundance of the *Firmicutes* phylum and a decrease in the relative abundance of the *Bacteroidetes* phylum. However, studies in humans have not corroborated this specific pattern: Some studies have observed a decrease in *Bacteroidetes* (but not an increase in *Firmicutes*) associated with obesity (7, 126), whereas others have observed the opposite (18, 100) or have not observed either of these phylum-level associations with body-mass index (BMI) (26, 35, 64, 122). In addition, studies have identified different genus- and species-level taxa associated with BMI or obesity (86, 132). Future downstream experimentation in animal models and humans can establish whether these candidate taxa play an etiologic role in obesity and, if so, suggest interventions for obesity prevention and treatment. Because of the potential to modify bacterial communities through various therapies (e.g., probiotics, prebiotics, antibiotics), the microbiome is an enticing candidate to target for the prevention and treatment of obesity.

4. ENVIRONMENTAL DETERMINANTS OF THE HUMAN MICROBIOME

4.1. Macroenvironment

4.1.1. Toxicological and chemical environment. The orodigestive tract and the respiratory system are major pathways for entry and processing of environmental toxicants in the human body. The rich metabolic repertoire of the human microbiome in these organ systems has a broad capacity for transformation of xenobiotic chemicals, sometimes opposite of the host patterns of biotransformation (1, 52). While oxidation and conjugation for excretion are typical of host metabolic enzymes, the microbial enzymatic reactions involve mainly reduction and hydrolysis (111, 136) and demethylation to generate carbon sources for further growth and division (113). Environmental arsenic speciation is related to cardiovascular disease and other health effects; evidence suggests that the methylation capacity of the microbiome resident in the orodigestive tract may influence these toxicities (16). Immobilization of metals, such as cadmium and lead by a gut *Lactobacillus*, may impact metal toxicities (20). Certain gut bacteria express azoreductase enzymes to metabolize potentially mutagenic azo compounds (141). Environmentally persistent chemicals from personal care products, such as triclocarban (3,4,4,9-trichlorocarbanilide, or TCC) and triclosan [5-chloro-2-(2,4-dichlorophenoxy)phenol, or TCS], are ubiquitous and linked to potential shifts in the microbiome in rodents (42). Microbial metabolism of chemicals including endocrine disruptors by gut microbiota can be accompanied by microbial dysbiosis: a change in the microbial community structure, the induction of specific bacterial genes, and altered microbial transformation of molecules (82, 94). In addition, endocrine disruptors can be absorbed and transported to

the liver, where they are conjugated and excreted back into the gut through bile secretion for further microbial metabolism (129). Enzymes such as azoreductases, esterases, methylases, thiolases, lipases, nitroreductases, β-glucuronidases, sulfatases, and β-lyases are also reported to be involved in the microbial metabolism of environmental chemicals (82, 94, 129).

4.1.2. Built environment and emerging hypothesis. The built environment comprises all structures built by humans, including our homes, workplaces, schools, and vehicles (36). Relying largely on microbial culture and other classic microbiologic techniques, investigators recognize that numerous microbial pathogens may be present in the built environment. For example, bacterial pathogens such as *Mycobacterium tuberculosis*, fungal pathogens such as *Aspergillus fumigatus*, and pathogenic viruses such as rhinovirus and influenza virus, and more recently severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes coronavirus disease 2019 (COVID-19), can be transmitted by direct inhalation in the built environment. Other pathogens, such as *Clostridium difficile* and *Enterococcus faecalis*, as well as norovirus and influenza virus, can be transmitted to humans through skin or mucus contact owing to fomite transfer from surfaces. In addition to direct microbial transmission, microbial metabolic products in the built environment may also be implicated in human health, including bacterial and fungal toxins, allergenic components of the cellular wall, and microbial-derived volatile organic compounds (15, 53). Indoor air and surfaces are associated with dust and microbial chemical products. Increased relative humidity in the environment results in an increase in microbial metabolites in dust and on surfaces. Indoor dampness and moldy conditions (for example, visible mold and mold odor) have been associated with many different disease states, but associations between the composition and concentration of microorganisms and their metabolites in the built environment and disease remain elusive. With the application of targeted bacterial 16S rRNA sequencing and whole-genome shotgun sequencing, researchers have gained a fuller appreciation of the complexity of the microbial ecology of the built environment, including the large diversity of culturable and nonculturable agents. Recognizing that the composition of microbial DNA sequences in an environmental sample may be composed of significant nonviable residue (30), environmental microbial-associated DNA exhibits a rich complexity reflective of human microbial sources, with a particularly strong relationship between the indoor built environment and human-derived microbial sources (103).

The concept of the hygiene hypothesis, which suggests that improved hygiene is possibly linked to the rise in autoimmune conditions, is adaptable to the concept of beneficial microbial exposure (28). Lax et al. (56) examined the correlative relationships between the human microbiome and the microbiome of the built environment, focusing on home environments and mapping the sharing of bacteria between occupants and their homes. This investigation demonstrated that the majority of bacteria associated with the surfaces had a significant probability of having originated from the occupants of that home. Exposure to a complex microbial community in house dust has been inversely associated with the likelihood of developing asthma (29). In another study, children who were exposed to household dust from homes immediately adjacent to a farming environment and who were actively working on the farm presented with a statistically significant reduction in the risk of developing asthma compared with children who were not exposed to farming environments (112). In summary, there is growing evidence of an interrelationship between the built environment, our microbiome, and health, yet much work is needed to understand the ecology and evolution of microorganisms in the built environment and human health.

Other notable hypotheses related to the built environment have emerged. One that is gaining currency in the literature is the rewilding hypothesis, which suggests that changes to urban green spaces that return them to a more natural state have the potential to change the microbiota in the environment and subsequently in human populations. Studies in humans and animals

demonstrated that rewilding may influence microbiome and host immune responses (101, 140). Among other environmental factors, work from 2018 suggests that inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome (71). Also, daylight exposure has been shown to modulate household dust bacterial communities, which may also implicate sunlight and UV radiation in human microbiome composition, for example bacterial communities on the skin (33). Climate change and extreme heat could also prompt physiological changes that might favor certain microbiota in the ambient environment, in food or within the body. Furthermore, in addressing the challenges of bringing together the multitude of microbiota with the myriad of established and emerging exposures, untargeted evaluations and discovery that couple bacterial metagenomics with environmental exposomics (130) may be one approach as part of a forward-looking research agenda.

4.1.3. Socioeconomic environment. Low socioeconomic status (SES) is associated with multiple health-related behaviors, such as reduced access to medical and dental care (6), increased engagement in unhealthy behaviors such as smoking and alcohol dependency (66), and decreased engagement in positive health behaviors such as healthy eating and exercise. Low-SES status is associated with higher rates of morbidity and mortality (105) and higher incidence of some of the health conditions previously mentioned in this review, such as obesity, diabetes, and cancer.

The role of microbiota in mediating these relationships between SES and health is under study (94). Many characteristics associated with low-SES neighborhoods and lifestyles (e.g., processed foods, sedentary lifestyle, psychosocial stress, exposure to pollutants and endocrine disrupters) are also associated with reduced gut microbial diversity (19). Studies have examined differences in microbial composition between high- and low-SES populations. In the United States, higher SES was associated with greater alpha diversity and population abundance of particular microbes in the gut microbiota (69). In other research, distinct differences in microbial composition were found between the gut microbiota of low-income children in Bangladesh and upper- to middle-class American children of the same age (60). Better understanding of the mediating relationship of the microbiome in SES-related disease susceptibilities will require integrative study that includes investigation of exposures at the community and individual levels. The built environment is one component under such consideration.

4.2. Microenvironment: Specific Environmental Exposures

4.2.1. Smoking. Cigarette smoke is a source of numerous toxicants (135), which come into direct contact with oral and upper respiratory bacteria; these toxicants can perturb the microbial ecology via antibiotic effects, oxygen deprivation, or other potential mechanisms (63). Loss of beneficial oral species due to smoking can lead to pathogen colonization and ultimately to disease; this contention is strongly supported by the well-established role of smoking in the onset and progression of microbially dependent periodontitis (76). Investigations in our lab (139) found decreased diversity in overall oral microbiome composition in current smokers and a lower relative abundance of the phylum *Proteobacteria* (4.6%) compared with never smokers (11.7%) (false discovery rate $q = 5.2 \times 10^{-7}$). The current smokers had decreased microbial abundance of genes associated with microbial aerobic metabolism pathways, including the tricarboxylic acid (TCA) cycle and oxidative phosphorylation, and increased abundance of glycolysis and other oxygen-independent carbohydrate metabolism pathways. Other pathways depleted in current smokers were certain xenobiotic biodegradation pathways relating to toluene, nitrotoluene, styrene, chlorocyclohexane, and chlorobenzene degradation and cytochrome P450 xenobiotic metabolism. Conversely, polycyclic aromatic hydrocarbon (PAH) and xylene degradation were

enriched in current smokers. These chemicals are components of cigarette smoke (93), and thus alterations in the oral community's ability to degrade these substances may have toxic consequences for the host. Aside from creating an anaerobic, acidic, and/or selectively toxic environment, smoking is also known to have prominent effects on human immunity (110), which can in turn influence the host's ability to stave off colonization by pathogens. In summary, increasing evidence indicates that smoking influences overall oral microbiome community composition and the abundance of many taxa; smoking may promote an anaerobic oral environment and a bacterial community with reduced xenobiotic degradation capabilities.

Observational and interventional studies (98) also suggest decreased diversity in the composition of the intestinal microbiome in smokers, generally demonstrating increases in *Proteobacteria* and *Bacteroidetes* phyla and *Clostridium*, *Bacteroides*, and *Prevotella* genera and decreases in *Actinobacteria* and *Firmicutes* phyla and *Bifidobacteria* and *Lactococcus* genera. Mechanisms that may explain the effects of smoking on the intestinal microbiome include oxidative stress enhancement, alterations of intestinal tight junctions and intestinal mucin composition, and changes in acid–base balance (98). Some smoking-induced alterations of the intestinal microbiome resemble those demonstrated in conditions such as inflammatory bowel disease and obesity. Further studies should be performed to investigate this connection. Smoking has an effect on the intestinal microbiome and is suggested to alter its composition. This interaction between smoking and the gut microbiome may contribute to the development of intestinal and systemic diseases.

4.2.2. Alcohol. Alcohol intake may impact the human oral microbiome in several ways: First, oral bacteria and fungi metabolize alcohol and dietary sugars to carcinogenic acetaldehyde (67, 73), interact with cigarette smoke condensate (102), produce carcinogenic nitrosamines (55), and experimentally promote oral carcinogenesis (78). The oral microbiota has a more potent ability to produce acetaldehyde from ethanol in smokers, both in vitro and in vivo (68, 96). In vitro and animal studies also point to possible mechanisms by which oral microbiota contribute to oral carcinogenesis, including inhibition of apoptosis, activation of cell proliferation, promotion of cellular invasion, induction of chronic inflammation (80, 84), and cooperation of bacteria and fungi in oral polymicrobial communities (41). Second, alcohol may yield direct cytotoxic effects on bacteria (46). Animal studies showed that 20% alcohol intake increases colonization by *Streptococcus mutans* (50) and dramatically decreases the number of detectable bacterial species in the oral biofilms of rats (48). In human studies, drinking red wine was associated with reduced species richness and a reduction in certain anaerobic bacteria in sub- and supragingival plaque (106), while excessive co-use of tobacco and alcohol was associated with reduced species richness and decreased abundance of *Neisseria*, *Aggregatibacter*, and *Fusobacteria* in oral mucosa biofilms (121). In addition to its direct effects, alcohol may indirectly impact the oral microbiota (31, 65, 99, 119) through disturbing the host defense system (77, 83, 114, 115), subsequently resulting in host-mediated periodontitis (11, 88). Large population-based studies have demonstrated that at least one standard drink per day increases periodontitis risk by 15–27% (88, 120) and links to poor oral health (49). Evidence shows that the oral microbiome is closely tied to oral health status (21, 117).

Alcohol and the gut microbiome have been studied largely in the context of heavy alcohol use, which may alter intestinal barrier function leading to gut leakiness, the production of proinflammatory pathogenic microbial products, and disturbed liver metabolic pathways (32). Studies in heavy users of alcohol and cirrhotics show that the relative abundance of bacteria from the phylum *Bacteroidetes* decreases as those from the phylum *Proteobacteria* increase and that individuals with cirrhosis exhibit a unique increase in *Fusobacteria* (17, 72). While heavy use of alcohol is related to intestinal dysbiosis, red wine, a rich source of dietary polyphenols, may, in moderation, favorably alter the gastrointestinal microbiota community composition. Red wine polyphenol significantly

increases the abundance of *Proteobacteria*, *Fusobacteria*, *Firmicutes*, and *Bacteroidetes*, whereas gin consumption significantly decreases these same bacterial phyla (91).

4.2.3. Dietary factors. The Western diet is characterized by the consumption of high fat, high sugar, high levels of red and processed meat, high levels of refined grains, and a lower level of fiber intake (22). Many studies have linked the Western diet to inflammation, diabetes, cardiovascular risks, obesity, metabolic syndrome (144), and cancer (8, 14). While a Western diet has a broad physiologic impact, influencing many different cell types such as adipocytes, immune cells, and endocrine cells, this diet is also strongly linked to shifts in the microbiome (79), characterized by lower microbial diversity and species richness (38) and an increase of the phyla *Firmicutes* and a decrease in *Bacteroidetes* (58). On a genus level, a Western diet shows a decrease in *Bifidobacteria* and *Lactobacilli*, while being high in *Enterobacteria* (107).

Fiber intake, in particular, is an appealing modifiable dietary factor, given its postulated beneficial biologic effects. Several studies have shown that fiber may be protective against conditions such as type 2 diabetes, cardiovascular disease, colon cancer, and obesity (25, 108). Fiber speeds colonic transit and may decrease exposure of colonic epithelial cells to ingested carcinogens. In addition, fiber undergoes fermentation by the microbiota to yield short-chain fatty acid end products, such as butyrate, which is essential for colon energy metabolism and epithelial proliferation and, in mouse models, exhibits tumor-suppressive activity through histone deacetylase inhibition (23). Consequently, there has been growing interest in understanding the impact of dietary fiber on gut microbiota composition, which may ultimately affect one's risk of cancer and other diseases. High-fiber diets are associated with higher gastrointestinal microbial richness and diversity and, in particular, are linked to a greater abundance of *Prevotella* and *Treponema*, as well as decreases in inflammatory signaling, protection against obesity, and possible decreases in the presence of colorectal cancer (109). Although short-term dietary intervention trials have demonstrated that different amounts of fiber intake can significantly alter microbiota composition in a span of a few weeks (79, 118), few studies in humans have evaluated the effect of long-term dietary habits of fiber intake on the gut microbiota (137).

5. SYNTHESIS: THE MICROBIOME, THE ENVIRONMENT, AND HEALTH

Research is advancing on the relationship in human populations between the environment, in a broad sense, and microbiome composition. Advances have also been made in identifying microbial components related to a variety of noncommunicable diseases and conditions. Building on this base, investigators are beginning to investigate more comprehensively the noncommunicable disease outcomes in relation to the interplay between the environment and the microbiome, with consideration of the role of the microbiome as both a target and a mediator of environmental exposure. Each of these three elements of an environmental science of the human microbiome and health are individually complex, presenting challenges for their integration. Environmental factors are often complex; the multitude of environmental factors to consider, let alone the ever-expanding understanding of the microbiome, make it difficult to grasp the full picture of how the external environment plays a causal role in disease incidence and mortality. In real-life settings, these factors often interact and are dynamic over time. Chemical toxicants frequently present in mixtures, as is the case, for example, with cosmetics and endocrine disruptors. Furthermore, exposures may vary throughout the life course as may age-dependent risks, conceptualized as windows of susceptibility. Owing to this complexity, it remains profoundly challenging to determine the microbial characteristics that directly or indirectly influence human health and disease.

New approaches will be needed to fully evaluate existing and as yet unknown factors that may influence the microbiome and human health. Prospective cohort studies are a mainstay of research on the environment and human health, particularly because this study design is important in establishing the natural temporal sequence of cause and effect, which is often difficult to disentangle in cross-sectional or retrospective research. Oral wash collections that are useful for oral microbiome assessment have been a component of cohort research for several decades; however, prospective collection of stool samples is only recently being developed. Similarly, collections for analyzing the human microbiome at other body sites and longitudinal collections of serial samples are only recently coming to a scale needed for epidemiologic research. Large population-based cohorts, which incorporate diverse racial, socioeconomic, and geographic groups with stool and oral microbiome specimens, are needed. Advances are also being made in experimental animal studies, with the development of germ-free (123) and humanized animal models, as well as simple animal models (24), such as zebrafish, *Drosophila Melanogaster*, and *Caenorhabditis elegans*. Also, advances in sample collection, identification, and extraction, in sequencing samples, and in data analysis have moved forward rapidly through initiatives such as the Human Microbiome Project (47) and the International Human Microbiome Standards project (**http://www.microbiome-standards.org/index.php**). Furthermore, the environment and the microbiome influence health status multidimensionally, which reinforces the need to integrate other 'omics, including metabolomics, transcriptomics, genomics, and immunomics. Relevant data integration tools and pipelines need to be developed.

In conclusion, this review has highlighted many of the factors in the environment that have associations with noncommunicable disease by influencing the human microbiome. We are clearly in an era when complex interactions, upstream causal factors, and multiple pathways of causation must be considered. Applying the results of these studies will be in the realm of individual modification of environmental factors, potentially involving microbial control, and in the realm of public policy, which is often more efficient for achieving changes that improve health. The challenge for microbiome science is to use observational epidemiology, exposure science, toxicology, and mechanistic studies to produce the best evidence possible for the betterment of population health.

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