The Human Microbiome and Health Inequities

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Individuals that are minoritized as a result of race, sexual identity, gender, or socioeconomic status experience a higher prevalence of most human diseases. Understanding the biological processes that cause and maintain these socially driven health inequities is essential for addressing them. The gut microbiome is strongly shaped by host environments and affects host metabolic, immune, and neuroendocrine functions. Therefore, the gut microbiome represents an important pathway via which environmental differences caused by social, political, and economic structures can be translated into inequities in health. Nevertheless, few studies have directly integrated the microbiome into investigations of health inequities. This review explores how taking into account host-gut microbe interactions can improve our understanding and management of health inequities. The authors start by outlining environmental influences on the gut microbiome and its development. They then explore microbial roles in health through the lenses of host metabolism, the immune system, and the nervous system. Finally, they emphasize the importance of changes in policy at multiple levels of government that account for the microbial role in health inequities. Overall, the researchers argue that studying the gut microbiome in minoritized populations will provide important insights into the biological mechanisms of health inequities and that health policy must shift to incorporate microbiome dynamics moving forward.

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1. Introduction

Inequities in disease morbidity and mortality among populations in the U.S and globally are a persistent public health concern. Some of these disparities trace to underlying socioeconomic inequities, which have increased over time with wealth accumulation and the increased potential for an unequal distribution of resources (1-3). For example, individuals classified as poor in the United States have nearly double the prevalence of diabetes compared with high-income counterparts (4). Similarly, individuals with less than a high school education have double the risk of obesity compared with college graduates (4). However, there is mounting evidence that inequities in health cannot be attributed exclusively to socioeconomic factors (5, 6). Self-identified race, sexual identity, and gender status are powerful predictors of health (7-10). For example, Black children have twice the probability of being re-hospitalized for asthma within 12 months of initial admission (11), Latino adults have twice the prevalence of diabetes compared to the U.S. average (12), and LGBTQ adults are more likely to be at risk for cardiovascular disease and to be diagnosed with asthma than heterosexual individuals (10).

Beyond other factors, health inequities in minoritized populations are believed to reflect influences of racism and discrimination. These influences include personal experiences of racism and discrimination that result in stress or trauma (13, 14)(Fig. 1). Importantly, they also include structural racism and discrimination that operates through laws, policies, and practices effected at multiple levels (14-16)(Fig. 1). These structural forces hinder equal access to basic resources such as health care, employment, education, and housing (6, 17-20). One result is segregated neighborhoods with reduced access to markets selling fresh, unprocessed foods, limited space for safe physical activity, and increased exposure to noise or chemical pollutants, among other health risks (17, 21). While these factors can negatively influence health directly, they also have
indirect effects. For example, racism, discrimination and segregation create chronic stress, which, together with associated behaviors such as interrupted sleep or alcohol consumption, is a salient influence on many health outcomes, particularly those related to cardiovascular diseases and mental health (22, 23). Discrimination can also undermine health seeking behaviors and treatment adherence due to lack of trust in health care providers and negative perceptions about the quality of health care services (24).

The impacts of socially-determined environments on health are likely to operate on multiple timescales. Specifically, the developmental origins of health and disease (DOHaD) literature suggests that exposures to early life adversity during sensitive periods of development both *in utero* and during the first two years of life can increase risk of developing disease later in life (25-27). These processes introduce the potential for intergenerational impacts of environmental exposures on health inequities.

Despite clear links between structural racism/discrimination, environments, and health inequities, gaps remain in our understanding of the biological mechanisms through which socially-determined environments impact health both within and across generations. For example, while chronic inflammation is often invoked as an underlying cause of many health inequities (28, 29), the specific processes driving inflammation have not been fully elucidated. Similarly, questions remain regarding how these physiological states are passed from one generation to the next.

The gut microbiome (GM)—the community of microbes that inhabits the human gastrointestinal tract—represents a novel pathway through which to explore environmental impacts on human biology and health in the context of health inequities. The composition and function of the GM is strongly shaped by host lifestyle and environment (30-35), and contribute
to host health by conferring protection from pathogens through colonization resistance and influencing host nutrition and metabolism, immune training and function, and brain development and behavior (36-42). Alterations to the GM can lead to immune, metabolic and neuroendocrine dysregulation characteristic of many pathologies. These alterations have been associated with a range of diseases including gastrointestinal infections, inflammatory bowel disease, obesity, diabetes, atherosclerosis, multiple sclerosis, autism, Parkinson’s disease, asthma, allergies, depression, and anxiety (43-53). In particular, reduced GM diversity is consistently linked to many chronic diseases (54). Although causality can be difficult to establish, in some cases, there is evidence that altered GM composition and/or reduced diversity directly cause disease (51, 55).

Given that the prevalences of many chronic diseases associated with an altered GM are higher in minoritized populations, alterations of the GM represent a potentially important pathway by which socially-driven health inequities could be biologically established and/or reinforced (Fig. 2). Nevertheless, there is currently a dearth of research directly investigating this possibility. Several studies have reported associations between the gut microbiome and socioeconomic status (56-58), as well as ethnicity and recent immigration (59-61), with many detecting lower gut microbial diversity in minoritized populations. Increased integration into industrialized economies and alterations in housing type have also been associated with reduced gut microbial diversity (35). Additionally, some host-GM interactions have been shown to vary with host socioeconomic status. For example, one study reports that the influence of maternal obesity on the infant gut microbiome is greater in populations with higher socioeconomic status (62). Aside from these exceptions, the potential role of the GM as a biological pathway linking political and economic policy, environment, race/ethnicity, sexual identity, gender, and socio-
economic status to health inequities is largely unexplored, although there have been recent calls for more attention to this area of study (63, 64).

In this review, we explore current research focused on the GM to identify its potential role in contributing to and perpetuating health inequities. We begin by examining the importance of the host environment in governing GM assembly. We then explore the potential role of the GM in maintaining health inequities in nutrition and metabolic diseases, asthma, and cognitive development and mental illness. We also comment on the potential role of the microbiome in perpetuating health inequities in COVID-19 morbidity and mortality. We review current strategies that may be used to manipulate the GM and consider their potential utility for addressing health inequities, before concluding with a discussion of both the challenges and opportunities for applying GM research to the study of health inequities and the implementation of public policy.

2. Processes governing microbial assembly

To understand whether health inequities are modulated by the GM requires an understanding of the processes by which microbial communities assemble during development and across adulthood. Infants are typically first exposed to microbes at birth, and many of these microbes will be of maternal origin (65-70). Delivery mode can modify an infant’s initial microbial exposures. The most persistent effect appears to be a delayed expansion of stably colonizing *Bacteroides* in the gut of C-section versus vaginally delivered infants (70-73). After birth, practices such as skin-to-skin contact and breastfeeding offer further opportunities for microbial exchange between mother and child (74, 75). While breast milk contains bacteria, it also contains oligosaccharides that stimulate the growth of potentially beneficial microbes (76-
At three months, babies that are breastfed have a distinct GM compared with babies that are formula fed, including lower microbial diversity and increased relative abundances of beneficial microbes (81-83), showing the influence of diet and breastfeeding duration on the infant microbiome.

In addition to these factors, infant physiology can also affect the established GM. Neurohormones such as dopamine and norepinephrine, as well as hormones, such as estrogens and glucocorticoids, have been shown to impact GM composition and function (84). Animal models provide evidence for the role of stressors as well. Six-to-nine-month-old rhesus macaque (Macaca mulatta) infants separated from their mothers show stress-indicative behaviors (e.g. distress calls), increases in plasma cortisol, and a significant reduction in fecal lactobacilli starting the third day after separation (85). Similarly, rats and chicks exposed to stress from heat and crowding possess a distinct GM compared with individuals not exposed to these stressors (86). While genetics may mediate some of these interactions as a result of their impact on host physiology, data linking the GM to host genetics in infants do not currently exist in the literature.

The infant’s social network (e.g. mother, babysitter, extended family, pets, daycare), physical environments (e.g. housing type, access to outdoor areas, pollution), and caregiver hygiene practices (e.g. water source, food preparation, bathing frequency, use of household cleaning chemicals) could also influence infant microbial exposures (87, 88). Variation in infant experiences with these factors is likely great. However, few data are currently available describing the effects of differences in infant rearing on establishment of the GM.

As infants mature, GM composition stabilizes, and by approximately three years of age, the GM is believed to resemble that of an adult (82, 89). Similarly to infants, a range of factors can affect the adult GM. For example, diet has a marked impact on the GM and can change GM
composition on timescales from hours to years, primarily as a result of differences in the availability of nutrients and the competitive relationships between microbes (89-94).

Other environmental factors shape GM composition in adults as well. High levels of perceived stress have been associated with differences in microbiome composition in adults (95, 96), and in laboratory animals, exposure to stressful challenges leads to shifts in microbial community composition (97-100). Additionally, other lifestyle factors such as sanitation and medical practices have marked impacts on the microbiome (101, 102). A study in South America also found that housing type is associated with variation in the microbiome, likely as a result of variation in exposure to outdoor environmental microbial communities (35). Therefore, while the adult GM is generally considered to be relatively stable, its composition and function are affected by factors that are likely to differ by socioeconomic status, ethnicity or self-identified race, sexual identity, or gender.

Beyond environmental factors, host genotype has been associated with variation in the GM and may play a role in structuring individual and population variation in GM-related disease (103-107). However, only a subset of the GM is related to host genotype in adults (108). Therefore, environmental factors appear to play the strongest role in shaping the human GM (31).

Although the gut microbiome exhibits some plasticity throughout life, gut microbiome dynamics in infants are likely to be particularly important given emerging evidence that not only what microbial taxa and genes establish, but when, matters to the long-term disposition of immune, metabolic, and neurological states (36, 109, 110). For example, it has been shown that mice that are not exposed to key microbes such as Lactobacillus, Bifidobacterium infantis, and Bacteroides fragilis during early life do not develop appropriate immune and nervous function
Likewise, mice exposed to low-dose antibiotics during early life exhibit altered metabolism and immune function even after their microbiome returns to its original state (115). These outcomes are believed to be a result of the absence of microbial signaling to host tissues either directly or through the production of key metabolites.

Finally, given the potentially strong impact of the maternal GM on the infant GM, intergenerational patterns of microbiome composition must also be considered. For example, mice fed a low fiber diet lose microbial taxa associated with fiber degradation across their lives (116). When offspring are fed the same diet, there is a cumulative intergenerational loss of microbial diversity and a shift away from fiber-degrading microbes. In another study, intergenerational microbiome transfer from mother to pup induced inflammatory bowel disease (117). To the extent that findings in mice apply to humans, the determinants of GM composition and its impact on health could therefore operate cumulatively across generations.

3. The potential role of the gut microbiome in perpetuating specific health disparities

Because a wide range of environmental factors can influence the early establishment and lifelong maintenance of the GM, socially-induced variation in these exposures across populations and individuals is likely to influence disparities in downstream health conditions. The GM has already been causally linked to some chronic diseases (51, 55), but studies that explicitly evaluate disparities in microbiomes and related health conditions are scarce. Here, we explore the potential role of the GM in establishing and perpetuating disparities in health conditions related to under-nutrition, metabolic disease, asthma, neurological development, and mood disorders. We also explore the recent COVID-19 pandemic.
**Child Undernutrition**

Child undernutrition affects more than 50 million individuals under five years of age and contributes to nearly half of all global child deaths (118). Severe cases are surprisingly refractory to recommended nutritional-based therapies, with long-term sequelae that include stunting, decreased earning potential, impaired vaccine response, increased risk of obesity and metabolic disease, and cognitive deficits (119-121). Furthermore, undernutrition is disproportionately prevalent in low-income and minoritized populations, even within high-income countries (122).

Undernutrition is believed to have multiple biological causes, including both macro- and micro-nutrient deficiencies. In low resource settings, common infections that decrease nutrient absorption and assimilation while simultaneously increasing immune energy needs are among the primary causes of undernutrition (123). In the case of diarrheal illnesses, exposure to pathogenic microbes can also alter the gut microbial community (124). Accordingly, the degree of undernutrition often directly correlates with enteropathogen burden and the frequency of diarrheal illnesses (123). Therefore, inequities in the burden of undernutrition-related diseases are likely to be strongly associated with structural variation in population exposure to enteropathogens, and thus conditions related to sanitation and availability of safe, treated water.

However, other mechanisms may also be at work. First, the GM influences the establishment of enteropathogens by reducing their success via competitive exclusion or pathogen-defense functions (42). Second, even in the absence of known pathogens or overt diarrheal disease at the time of sampling, undernourished children have abnormal GMs (121, 125-129). For example, while GM configurations develop and mature in a predictable pattern as a function of a healthy child’s age, this pattern of GM maturation is impaired in acutely undernourished children (121). Results from recent studies highlighted a causal link between the
dysbiosis of undernutrition and growth impairment (126, 127, 129). Bacteria isolated from the stool of malnourished children, compared with those derived from healthy children, can exacerbate weight loss and worsen infections in inoculated gnotobiotic mice (128), and these phenotypes can be resolved in both mice and piglets through the use of microbiota-directed foods (130). Similarly, accelerated ponderal and linear juvenile growth are observed in mice receiving specific strains of the Lactobacillus plantarum (131). Although mechanisms underlying these causal links remain speculative, they appear to involve altered host metabolism in multiple organ systems, including the liver and brain.

Multiple factors likely drive the microbial patterns associated with child undernutrition and stunting. In addition to the effects of environmental exposure on pathogenic microbes, low diversity diets that are high in specific carbohydrates may provide a selective advantage to microbes capable of metabolizing these substrates, and can result in a less diverse GM.

Inflammation, a hallmark of the intestinal pathology that underlies many cases of child undernutrition, can shape the GM by inducing secretion of host anti-microbial peptides, generating reactive oxygen and nitrogen species, and disrupting the mucosal oxygen gradient, which regulates spatial microbe distribution (132-134). Other potential mediators of the dysbiosis associated with undernutrition include maternal, prenatal, perinatal and genetic factors, as well as functional impairments of the liver, pancreas, immune and endocrine systems (135, 136). Several of these factors are likely to more strongly affect specific human populations, thereby facilitating inequities in microbial development. For example, children living in urban food deserts may not have access to fresh produce and other high-fiber diet items that can increase GM diversity and resilience. Similarly, mothers of infants in low socioeconomic or minoritized neighborhoods may shift from breastmilk to formula earlier in life as a result of
maternal work pressure, or lack of culturally and contextually relevant health information to support initiation and maintenance of breastfeeding (137). The combined loss of protective microbial factors in breastmilk and increased exposure to waterborne pathogens—and toxins such as in Flint, Michigan (138)—may put such children at higher risk for microbial dysbiosis and ultimately undernutrition. Although children in these neighborhoods may often have higher rates of undernutrition (139), few studies have explored a direct role of the GM (140).

Diseases related to overnutrition

More than half of the world’s adult population is now considered overweight or obese, and the related conditions of diabetes and cardiovascular disease are now the leading causes of death globally (141). The rise of these conditions has been particularly rapid in developing economies experiencing transitions toward sedentary lifestyles and high-calorie diets (142), as well as in minoritized populations with limited access to affordable fresh produce and safe spaces for physical activity (143). In the U.S., more than one out of every three people is considered obese (144), with prevalence disproportionately biased towards populations with reduced economic stability, lower levels of education, limited access to health and health care services, and those living in minoritized and segregated neighborhoods (143).

While an imbalance between energy intake and energy expenditure is crucial to the development of these conditions, it is unclear why individual populations vary in their susceptibility to the adverse health effects of these lifestyle changes (141). The GM is one potentially important pathway since it has been shown to have a causal effect on obesity (51). There are multiple mechanisms through which the GM appears to affect host metabolism, including excess energy production by the gut in the form of short-chain fatty acids (SCFAs),
metabolic programming by the GM via production of SCFAs or other metabolites, and promotion of inflammation by the GM (51, 145-150). Although findings conflict somewhat across studies, changes in GM composition and function that signal a potential role for these pathways have been observed in multiple human studies. Similar to other chronic diseases, a general finding is that a low diversity GM with altered microbial composition is associated with increased risk for obesity and diabetes (51, 151-153). As such, early life environments that promote these microbial traits may lead to the establishment of obesogenic GMs in some human populations.

As with undernutrition, there are multiple potential drivers of reduced GM diversity and altered composition during different stages of life that are likely to be patterned in response to social inequities. Cesarean births and formula feeding have been associated with both altered GMs and increased prevalence of metabolic disease (71, 154-156) and tend to be more frequent in low-income and minoritized populations (137, 157, 158). Once solid foods are introduced, diets with reduced fiber content are likely to lead to overnutrition, not only as a result of nutritional intake but also as a result of their impacts on the GM. For example, diets high in fat and sugar, and low in fiber, are consistently shown to result in GMs that share traits with those that cause metabolic disease (159). Low-income and minoritized families tend to rely heavily on these types of diet as a result of both geographic and economic accessibility (160, 161). Finally, antibiotic use has also been suggested to be an important potential driver of reduced GM diversity and increased host adiposity. Studies with both mice and humans have shown that increased exposure to antibiotics during infancy leads to increased risk for high BMI and metabolic disease later in life, particularly for children of lean mothers (117, 162-164). In the U.S., lower income populations are generally prescribed antibiotics at higher rates (165).
Many of the same mechanisms are likely to mediate disease risk in adult populations, but additional factors are important to consider as well. For example, dysregulation of host sleep and circadian biology has been linked to obesity and metabolic disease (166-169). GM circadian rhythms interact with host circadian rhythms (170, 171), and various forms of sleep disruption alter the GM (172, 173) (but see (174)). Therefore, individuals with unusual sleep-wake cycles, such as shift workers, may be particularly prone to altered GM composition and related health outcomes. Given that shift work is often disproportionately prevalent in minoritized populations (175, 176), these findings represent another pathway through which GMS may mediate health inequities.

Finally, it is possible that metabolic disease phenotypes are being transmitted intergenerationally via the GM. Some studies have suggested that transmission of obesogenic GMs between mother and infant at birth may alter the infant GM and increase susceptibility to metabolic disease later in life (177-179). Therefore, mothers with metabolic disease as a result of socially-influenced GM dynamics may pass on disease risk to their offspring, regardless of the actual social and microbial environment the offspring are born into. Although these intergenerational processes are possible for all GM-mediated diseases and therefore must be considered in all contexts, thus far, the best data exist in the context of metabolic disease.

Asthma

Asthma affects approximately 14% of children worldwide with incidence increasing by 50% every decade (180). In addition to its role in mortality, the impact of asthma includes wide-ranging factors like days lost from school, interference with physical exercise, and under-functioning at school because of interrupted sleep (181, 182). While asthma occurs in all countries regardless of level of development, more than 80% of asthma deaths occur in low and
lower-middle income countries (180). It also disproportionately impacts low-income, minoritized, and inner city populations in middle- and high-income countries (180), making it a major contributor to health inequities.

Although genetic susceptibility contributes to asthma pathogenesis, it only explains a minority of cases while the rapid rise in prevalence clearly points to an important role of changing environments and lifestyles (183). Studies in industrialized countries have shown that growing up in a rural/farm environment protects children from developing immune-mediated and inflammatory diseases, such as asthma, hay fever and eczema (183-185). Helminthic infections during childhood have also been shown to protect against future development of atopy and respiratory symptoms, pointing to a likely role of reduced exposures in the etiology of the condition (186). Additionally, vaginal birth, breastfeeding, and household pets have been identified as potential protective factors (187-190). In contrast, being exposed to antibiotics during late pregnancy and the first year of life predicts an increase in the risk of developing asthma (189, 191, 192). Likewise, respiratory viral and bacterial infections, as well as mold sensitization, have been consistently associated with asthma in most epidemiological studies that recorded these variables (193, 194).

Collectively, these findings support the notion that microbial exposures during childhood act as a powerful stimulus that drives alterations in the development of the immune response (189, 195). Consistent with this interpretation is the finding that microbial alterations have been observed in the airways of individuals with asthma (196-198). Although causality cannot be determined from these cross-sectional studies, mounting evidence shows that alterations in the infant GM predict increased risk of asthma development later in life, potentially as a result of their pro-inflammatory effect on the host immune system (53, 199, 200). For example, in the
prospective CHILD study, four gut bacterial genera \((Faecalibacterium\ spp., Lachnospira\ spp., Veillonella\ spp.\ and\ Rothia\ spp.)\) were negatively associated with future asthma development in 3 month-old infants (53). Notably, supplementation of these bacterial taxa to germ-free mice colonized with stool samples of a 3 month-old that went on to develop asthma at school age, significantly ameliorated airway inflammation, emphasizing the immunomodulatory capacity of these bacteria (53).

As a result of these findings, it seems likely that inequities in environmental microbial exposures are a causal biological factor underlying disparities in asthma development. As mentioned previously, rates of vaginal birth and breastfeeding are often lower in low-income and/or minoritized populations (137, 157, 158). Also, urban populations may have reduced exposure to animals, outdoor or environmental microbes, and in some cases, gastrointestinal parasites. All of these factors could result in an altered GM and increased risk of asthma. In contrast, exposure to protective factors, such as gastrointestinal parasites or domestic animals, may be more prevalent in some rural communities with low socioeconomic status that are often thought to be at higher risk for other health issues. It is not surprising then that incidences of asthma tend to be lower in rural, low socioeconomic status communities (183-185, 201). Nevertheless, exposure to infectious disease and/or specific asthma treatment regimens may alter the severity of asthma among high-risk individuals in otherwise low-risk populations via effects on the GM. Therefore, additional studies of the complex interaction between the GM, asthma outcomes, and host environment and behavior are necessary.

**Preterm birth and neurodevelopmental trajectories**

Despite technology-enabled increases in the survival of extremely preterm (<28 weeks)
infants in the US, surviving extremely low birthweight infants have high rates of neurodevelopmental disability that are inversely proportional to gestational age at delivery, and 30-40% of survivors have cognitive scores more than two standard deviations below the mean (202, 203). However, neither gestational age nor birth-weight alone can fully predict the long-term neurodevelopmental outcomes of extremely preterm infants. Environment appears to play some role. Preterm babies born into low socioeconomic status families and/or minoritized populations often have poorer outcomes (204). For example, preterm infants born to low-income families show less improvement in cognitive scores at two years of age and beyond (205, 206).

While a number of factors, including access to early life education (207), likely contribute to the health outcomes of pre-term infants, recent work suggests a role for the GM. Gnotobiotic mice colonized with the GM from human preterm infants experience alterations in inflammatory phenotype, including elevated systemic inflammation, as well as alterations in myelination, neuronal number, and neurotransmission pathways (208). Inflammatory profiles have been proposed as a mechanism for altered brain development and poor neurodevelopmental outcomes in other perinatal circumstances such as maternal obesity (209) as well as in animal studies (210, 211). Thus, microbial communities that influence inflammatory phenotypes could alter neurodevelopmental outcomes. Other studies have demonstrated that the GM of infants is linked to neurodevelopment at one year of age (212).

It follows that the observed effect of social influences on neurodevelopmental outcomes in pre-term infants may be at least in part a result of variation in GM exposures (213). Given that low socioeconomic status, race/ethnicity, sexual identity, and gender are correlated with altered exposure to food resources, social stress, environmental exposures, and other factors that affect the GM, preterm infants born to mothers of low SES or minoritized populations may be exposed
to distinct maternal GMs. Additionally, parental ability to engage with infants in the neonatal intensive care unit via skin-to-skin contact and/or breastfeeding as a result of professional or personal demands, or infant health status, may also result in differences in infant microbial exposures. Finally, once infants can be brought home, in minoritized and segregated neighborhoods, the same factors that are likely to have influenced their mother’s microbial exposures can operate on the infant, further altering the GM and exacerbating neurodevelopmental trajectories. Nevertheless, few data are available to investigate these relationships.

Mental health

Mental illness is recognized as one of the largest causes of morbidity globally (214). Depression is the leading cause of disability worldwide, and approximately half of those diagnosed with depression also suffer from anxiety simultaneously (215). Individuals belonging to minoritized populations as well as individuals with reduced economic resources are disproportionately impacted by these conditions (2, 216-218). For example, LGBTQ individuals are 2.5 times more likely to experience depression and anxiety, compared to heterosexual individuals (219), and Black children are more likely to visit the emergency room for mental health concerns than white children (220).

There are a number of factors that may affect the emergence of mental illness. In some cases, genetic differences increase risk by altering the production and detection of neurotransmitters and/or inflammatory profiles (221, 222). More commonly, environmental factors such as stress and diet strongly influence symptoms of depression and anxiety (223, 224). For example, adolescents exposed to family discord and stress are more likely to exhibit
depressive symptoms (225). In other contexts, consumption of non-refined grains and vegetables has been shown to have a preventative effect on anxiety and depression (226). However, little is known about the specific biological processes via which socially-induced environmental disparities in stress, diet, or other factors affect mental health outcomes.

The GM is emerging as a potentially important mediating pathway linking social environments to mental illness. In both humans and rodents, individuals with symptoms of depression have distinct GM compositions compared with individuals without symptoms (227, 228). Given that stress and diet can alter the GM, it is possible that these patterns are simply a reflection of host environmental variation and do not play a causative role in the emergence of symptoms. However, it is notable that a depressive phenotype can be induced in rats using a fecal transfer from depressed patients (229). Conversely, probiotics and prebiotics have been shown to ameliorate depressive symptoms in both animal models and humans (230-232).

Causal relationships between the gut microbiota and mental health may be associated with the ability of the GM to influence the metabolism of host neurotransmitters and hormones. For example, the GM affects the production of serotonin, dopamine, and GABA, and can alter levels of ACTH and glucocorticoids (233-236). There is also evidence that gut microbes can directly influence nervous system functioning through interactions with sensory neurons, including the vagus nerve that connects the gut to the brain (237, 238). As a result, it may be that the roles of diet and stress in mental health are a function of the GM (239, 240). For example, GM shifts incited by either of these factors could increase gut permeability, allowing microbes normally contained in the gut to enter the bloodstream and trigger an inflammatory response that affects nervous system functioning. In fact, individuals with major depression have elevated serum antibodies to a number of gram negative bacteria (241, 242). These processes
may even operate on intergenerational timescales since chronic stress during pregnancy changes the maternal gut and vaginal microbiome (213, 243, 244). These alterations can incite inflammatory responses in the placenta and changes in the fetal brain prenatally (243, 244), or can be transmitted to offspring at delivery, potentially further impacting neurodevelopment (243-245).

Both personal experiences of structural racism and discrimination cause chronic stress in minoritized populations. While this chronic stress could be sufficient to trigger mental illness by itself, the GM may also play an important role in exacerbating and perpetuating symptoms across both life courses and generations. Minoritized populations exposed to high levels of chronic stress may undergo changes in the GM that promote nervous system dysregulation. These GM changes may be passed from parents to offspring, resulting in altered stress reactivity and susceptibility to mental illness across generations. Alternatively, other risk factors such as a low-fiber diet resulting from urban food deserts could alter the GM in a way that causes systemic inflammation and increased susceptibility to mental illness, independently of chronic stress. Additional research will help us tease apart these complexities.

**Infectious disease and the COVID-19 pandemic**

The COVID-19 global pandemic caused by coronavirus SARS-CoV-2 represents one of the most recent and acute examples of health inequities. Although everyone is susceptible to the disease, Black and Latino populations in the U.S. are exhibiting higher infection and mortality rates compared to their white counterparts (246, 247). These disparities are likely due to a combination of factors including limited ability to engage in isolating behaviors to reduce
exposure, such as working from home, increased probability of underlying comorbidities such as obesity, diabetes, and asthma, and reduced access to healthcare (246-248).

Although there is still much to learn about this virus and its interactions with hosts, it seems likely that the gut microbiome plays a role in shaping COVID-19 outcomes (249) and the observed inequities in those outcomes. To begin with, many of the underlying comorbidities that increase risk of morbidity and mortality from COVID-19 appear to be shaped by host-microbe interactions, as described previously in this review. Thus, the microbial dynamics that increase susceptibility to many chronic diseases also increase risk of poor outcomes in the context of SARS-CoV-2 exposure. Additionally, the gut microbiome is known to train the immune system during infancy and affect immune function throughout life (36, 38). These dynamics have been shown to affect host responses to other respiratory viruses such as influenza virus (250, 251), and likely play an important role in dictating host immune responses to SARS-CoV-2. For example, COVID-19 mortality rates appear to be strongly influenced by host susceptibility to ‘cytokine storms’, which are out-of-control inflammatory responses, and the gut microbiome can directly influence host cytokine levels and inflammatory status (252-254). Finally, COVID-19 appears to infect the gut as well as the respiratory tract (255, 256), allowing the gut microbiome to more directly affect the trajectory of the disease. Individuals with reduced gut microbiome diversity, increased prevalence of opportunistic pathogens, and/or reduced relative abundances of anti-inflammatory microbes are more likely to experience reduced gut barrier integrity and have an increased potential for severe disease and its complications, including cytokine storms and sepsis. As described earlier in this review, individuals in minoritized populations are more likely to exhibit these gut microbiome traits as a result of the physical and social environments that they are exposed to throughout life. Therefore, while the COVID-19 pandemic has highlighted a
range of non-microbial mechanisms through which health inequities operate, the gut microbiome may prove to play an important role as well.

4. Addressing Microbial Health Inequities

Microbiome-targeted interventions

Given the clear potential for the GM to contribute to a range of health inequities, it is important to consider how the GM might also be utilized to reduce health inequities. Because it appears that the GM is a mediating factor in many diseases, and because every individual has a unique GM, the use of GM research to inform targeted health interventions, including personalized medicine approaches, has recently received growing attention. For example, *Lactobacillus* and *Bifidobacterium* probiotics are being used in multiple clinical trials as a treatment for depression with mixed outcomes (257), and fecal transplants are a highly effective therapy for *C. difficile* infection (258, 259). Nevertheless, substantial research is necessary before these approaches can be routinely implemented. Even in the relatively simple case of probiotics, the microbial taxa of interest only establish in the gut in a subset of people, and it remains unclear whether this establishment is actually beneficial to health (260, 261). Additionally, interventions that depend on targeting specific microbial taxa may be difficult to develop given that microbial strains that are minimally genetically distinct from each other may interact with hosts distinctly (262). Therefore, efforts may need to focus on microbes that have large positive effects on their host (263). For instance, *Bifidobacterium longum infantis* in breastmilk synthesizes vitamins (264), releases compounds that protect babies from pathogenic bacteria (265, 266), and positively affects immunological responses (267). Therefore, interventions fostering *B. infantis* are likely to have a stronger effect than interventions targeting other
microbial taxa in infants. Research is underway to identify key microbial taxa in other contexts, such as malnutrition (125, 130). Alternatively, researchers should look past microbial taxonomy to identify specific microbial genes, proteins or metabolites that are associated with particular beneficial or detrimental effects. For example, a particular GM gene was recently identified as central to the ameliorative effect of green tea on type 2 diabetes (268).

However, even with substantial research advances that improve efficacy, these types of personalized treatments and interventions are likely to be inaccessible to many of the populations suffering disproportionately from the targeted diseases (Fig. 3). First, quite simply, these treatments are likely to be cost-prohibitive for low-income populations, particularly during early stages of development. Furthermore, the environmental factors that create the foundation for high rates of chronic disease in minoritized populations are driven by broader political and economic forces (2, 5, 24). These same structural forces not only foment environmental health risks, but also impede access to health care. Therefore, it is unlikely that the minoritized populations that would most benefit from personalized microbial medicines will have an opportunity to use them.

**Microbially-driven health policy**

Given the current limitations of microbial therapies that target specific taxa or genes in specific health contexts, as well as the fact that they are likely to be distributed through the same structurally-biased systems that underly health inequities, policy interventions targeting the political structures and environments associated with altered GMs may be our most effective tool presently, both in terms of cost and magnitude of impact (Fig. 3). If we can reduce differences in the types of microbes that populations are exposed to by providing resources to facilitate
behaviors such as fiber consumption that are associated with 'beneficial' GMs, this could positively impact the multiple dimensions of health inequities that we reviewed above. Although future research will be necessary to optimize these approaches, existing knowledge of environmental impacts on the GM already provides an important foundation upon which new policy perspectives can be built as the field advances (Fig. 2).

Importantly, policies that are beneficial for GM health can likely be developed from existing initiatives, because many health policies already target politically- and socially-driven variation in resource distribution patterns and environments (143). However, because current policies almost universally do not consider the GM, there are likely to be critical gaps in their effectiveness. Explicitly integrating knowledge of the environmental drivers of GM ecology into both new and existing policy at local, state and federal levels (6, 269) is likely to substantially improve associated health outcomes.

Health policies aimed at promoting breastfeeding are an excellent example. In many global settings, low SES and/or minoritized population status has been associated with a lower tendency to breastfeed (137, 157, 270-272). These patterns are, in part, a result of long work hours in jobs without infrastructure to support breastfeeding and limited culturally-relevant and accessible resources for promoting breastfeeding (273, 274). In addition to benefitting infant nutrition and maternal and infant social and emotional health, breastfeeding also facilitates the transmission of maternal microbes such as \textit{B. infantis} (275). Therefore, a lack of support for breastfeeding and decreased incidence of breastfeeding in any one generation could block transmission of \textit{B. infantis} and its attendant health benefits to subsequent generations. Programs to support breastfeeding for mothers in all environments (276, 277) have the potential to reduce health inequities through multiple mechanisms, including improved infant GM development.
However, existing policy could be adjusted to optimize GM development. For example, many current workplace efforts aimed at supporting breastfeeding in working mothers tend to focus on providing the space and resources for mothers to express milk. While this practice partially facilitates the infant GM development through the provision of breastmilk, it perpetuates the reduction of physical contact between mothers and infants, which may alter transmission patterns. It is also unclear whether freezing, thawing, and reheating breastmilk affects microbes and other bioactive human milk components (278). These dynamics provide a strong rationale for policy changes. Recent movements in the U.S. to guarantee a minimum period of paid parental leave, reflecting policies implemented in Canada and northern Europe, are likely to have substantial impact in this area of health, particularly if they advocate for the recommended six-month period of exclusive breastfeeding (279).

Similarly, policies that are aimed at reducing health disparities by improving access to affordable, non-processed foods in urban food deserts have potential to impact the microbiome. High-fiber diets have repeatedly been associated with specific GM traits that appear to promote positive health outcomes in hosts (94, 280-282), and some foods appear to be more effective probiotics (sources of microbes) and prebiotics (substrates that support microbial populations) compared with others (283, 284). Furthermore, dietary diversity is positively correlated with GM diversity, and high GM diversity is believed to be beneficial to host physiology and health (54, 285). However, existing policies tend to emphasize the nutritional importance of lean protein sources and fresh produce and do not recognize the role of food in shaping the GM and associated health outcomes. Educational programs targeting nutrition should incorporate this information to promote intake of ‘microbe-friendly’ foods at all ages, beginning as early as weaning. Simultaneously, markets that are introduced into food deserts should be designed to
more optimally benefit the GM by purposefully emphasizing probiotic and prebiotic foods as part of broader strategies of ensuring a wide diversity of fresh foods. Food banks and food supplement programs such as WIC in the U.S. should also improve access to these types of diets. Such efforts would be markedly more feasible with the design of fresh food production and delivery systems that are more efficient, flexible, and resilient to disruption than our current infrastructure (286, 287). Although our understanding of diet-GM interactions has to develop more before we can prescribe certain foods for certain GM communities and/or host health outcomes, some of the basic knowledge we already have can and should start to be integrated into these interventions.

As a final example, improved access to green space in neighborhoods has the potential to positively affect health by increasing exposure to diverse microbial communities (288, 289). However, many populations in industrialized urban centers currently have limited access to outdoor green spaces given the long hours spent in indoor work environments coupled with reduced access to safe, green spaces in low SES and minoritized neighborhoods (290). Policies aimed at increasing access to outdoor areas both at work and at home are likely to have important health impacts. Nevertheless, to effectively improve microbial exposure with these policies, green spaces must be carefully designed (289, 291). For example, playgrounds that incorporate features such as grass, woodchips, and sandboxes promote complex environmental microbial communities (Fig. 4). Play structures that further encourage child contact with these substrates during play and exploration are likely to facilitate exposure to these 'typical' environmental microbial communities. In contrast, play areas made with recycled rubber and plastic will promote exposure to 'artificial' microbial communities that interact in unknown ways with the human GM and health (Fig. 4). As a result, policies for establishing outdoor spaces
should prioritize natural features over more modern 'clean' designs to maximize the microbial benefits of these spaces.

These examples only scratch the surface on the potential avenues through which policy might improve health through impacts on the GM. However, they demonstrate the substantial overlap that exists in current policy initiatives and those that would improve microbially-influenced health challenges. Indeed, some policies are already driven by knowledge of microbial impacts on health such as antibiotic stewardship programs and improvements to water and sewage infrastructure to reduce exposure to enteric pathogens (292-294). As our understanding of the role of the GM in various health domains increases, we anticipate that this will inspire entirely new policy approaches to reducing the societal impact of major GM-related health issues. For instance, minimum outdoor recess time could be required at all daycares and elementary schools to increase exposure to environmental microbes, and information regarding the importance of this outdoor exposure could be shared with families more broadly to guide home practices. In conjunction with animal shelters, programs supporting prescribed exposure to a range of animals for children being raised in minoritized environments could be implemented to facilitate microbial transmission and counteract the negative microbial effects of stress, while simultaneously providing socialization opportunities for the animals. Or, the use of pasteurization at breastmilk banks could be improved to better preserve the microbial properties of breastmilk, and microbial traits could be used to best match donors and recipients. While all of these suggestions would require assessments of feasibility and risk, they represent novel ways in which we might reduce the burden of health disparities by targeting microbial pathways.

5. Conclusion
Continued communication between GM researchers, medical doctors, and policy makers at multiple levels should aim to refine and advance efforts to address health inequities through a microbial lens. Microbiome research alone will not eliminate existing health challenges, particularly given the severe biases and shortcomings in our healthcare systems that are increasingly visible (2, 6, 269, 295). Instead, sweeping policy reform that includes microbial perspectives has the potential to transform current health landscapes and substantially reduce health inequities if implemented carefully. Although more research is necessary to identify specific microbial taxa and genes that should be targeted by these policies to maximize health benefits, our existing knowledge of lifestyle practices that positively affect the GM and host health is sufficient to begin incorporating GM dynamics into policy decisions. Simultaneously, questions raised by policymakers considering environmental impacts on the GM may guide GM research more quickly toward topics of applied value in reducing health disparities.

In this spirit, we also argue that microbiome research must aim for a more expansive understanding of what is microbially 'healthy' or 'unhealthy'. For example, decreased gut microbial diversity is generally agreed to indicate a health risk, but reduced GM diversity is not always bad - as is evident in stool from healthy, exclusively-breastfed infants (69). Likewise, a biomarker signature found in healthy people of wealthy and/or industrialized societies that belong to a specific race/ethnicity, sexual identity, or gender will likely be different from a biomarker signature for other populations, given different host genetics, environmental exposures, dietary traditions, etc. Unless these differences are taken into account, future microbiome-based therapies and policy interventions may be ineffective in some populations, and these populations are likely to be the populations that are most vulnerable and face greater health inequities. Similarly, therapies ultimately must be accessible and affordable, locally and
sustainably produced, and both palatable and culturally acceptable. As a result, microbiome research must continue to become a more interdisciplinary endeavor (296), and perspectives from researchers in diverse populations must be considered when addressing health challenges (e.g. 297, 298). If microbial research and the resulting tools continue to be limited to more majoritized human populations, it will worsen the already alarming health disparities in worldwide disease burden. Therefore, the basic research underpinning the development of new therapies must include diverse populations and account for the rich cultural and environmental contexts within which people and their GMs exist.

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Figure 1. Racism and other forms of discrimination contribute to health inequities via two main pathways. (a) Personal experiences of racism and discrimination that result in stress or trauma. (b) Laws, policies, and practices that structurally hinder equal access to basic resources such as health care, employment, education, and housing.

(a) 

(b)
Figure 2. Socially-determined environments are likely to affect health via impacts on the gut microbiome across multiple life stages. Policies aimed at reducing health inequities should therefore consider host-microbe interactions to increase efficacy.

<table>
<thead>
<tr>
<th>stage of life</th>
<th>socially-mediated microbiome influences</th>
<th>potential policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-natal</td>
<td>• antibiotic exposure • breastfeeding rates • method of birth</td>
<td>breastfeeding support</td>
</tr>
<tr>
<td>infancy</td>
<td>• environmental microbial exposures • gastrointestinal parasites • diet</td>
<td>safe outdoor play spaces</td>
</tr>
<tr>
<td>childhood</td>
<td>• societal and economic stress • circadian rhythm perturbations</td>
<td>access to fresh, non-processed foods</td>
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<td>adulthood</td>
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Figure 3. Given that the gut microbiome is associated with many of the chronic diseases in which inequities are observed, it represents a potential target for intervention. Two distinct approaches to using the gut microbiome for reducing health inequities are (a) developing targeted microbiome therapies to prevent or treat specific diseases and (b) designing policies that address the environmental differences that contribute to microbiome alterations that increase disease risk. While there is excitement in the medical community with regard to the former, they are likely to be distributed through the same structurally-biased systems that underly health inequities and are therefore unlikely to have a strong impact on minoritized populations. In contrast, policy interventions that reduce or eliminate the structural biases that result in differential microbial exposures and microbiome assembly is likely to have a stronger impact on minoritized populations.
Figure 4. Although more research is necessary, playgrounds made with (a) recycled rubber and plastic are more likely to promote exposure to simple, 'artificial' microbial communities that interact in unknown ways with the gut microbiome and health while those that incorporate (b) features such as grass, woodchips, and sandboxes are likely to promote exposure to complex, ‘natural’ environmental microbial communities that are associated with positive impacts on the gut microbiome and health. Policies for establishing outdoor spaces should therefore prioritize natural features over more modern, 'clean' designs to maximize the microbial benefits of these spaces.