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The Human Microbiome and Health Inequities

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ABSTRACT

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, Parksinson'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 minoritzed 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-

80). 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

(38, 111-114). 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 *B.infantis* (275). Therefore, a lack of support for breastfeeding and decreased incidence of breastfeeding in any one generation could block transmission of *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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References

1. K. Flannery, *The creation of inequality: how our prehistoric ancestors set the stage for monarchy, slavery, and empire* (Harvard University Press, 2012).
2. A. Case, A. Deaton, *Deaths of Despair and the Future of Capitalism* (Princeton University Press, 2020).
3. N. E. Adler *et al.*, Socioeconomic status and health: the challenge of the gradient. *American psychologist* **49**, 15 (1994).
4. CDC (2013) CDC Health Disparities and Inequalities Report — United States, 2013. in *Morbidity and Mortality Weekly Report*.
5. K. B. Wilson, R. J. Thorpe Jr, T. A. LaVeist, Dollar for dollar: racial and ethnic inequalities in health and health-related outcomes among persons with very high income. *Preventive medicine* **96**, 149-153 (2017).
6. Z. D. Bailey *et al.*, Structural racism and health inequities in the USA: evidence and interventions. *The Lancet* **389**, 1453-1463 (2017).
7. N. Mulia, S. E. Zemore, Social adversity, stress, and alcohol problems: are racial/ethnic minorities and the poor more vulnerable? *Journal of studies on alcohol and drugs* **73**, 570-580 (2012).
8. G. H. Brody *et al.*, Perceived Discrimination Among A frican A merican Adolescents and Allostatic Load: A Longitudinal Analysis With Buffering Effects. *Child development* **85**, 989-1002 (2014).
9. M. King *et al.*, A systematic review of mental disorder, suicide, and deliberate self harm in lesbian, gay and bisexual people. *BMC psychiatry* **8**, 70 (2008).
10. K. J. Conron, M. J. Mimiaga, S. J. Landers, A population-based study of sexual orientation identity and gender differences in adult health. *American journal of public health* **100**, 1953-1960 (2010).
11. A. F. Beck *et al.*, Role of financial and social hardships in asthma racial disparities. *Pediatrics* **133**, 431-439 (2014).
12. N. Schneiderman *et al.*, Prevalence of diabetes among Hispanics/Latinos from diverse backgrounds: the Hispanic community health study/study of Latinos (HCHS/SOL). *Diabetes care* **37**, 2233-2239 (2014).
13. T. T. Lewis, C. D. Cogburn, D. R. Williams, Self-reported experiences of discrimination and health: scientific advances, ongoing controversies, and emerging issues. *Annual review of clinical psychology* **11**, 407-440 (2015).
14. C. J. P. Harrell *et al.*, Multiple pathways linking racism to health outcomes. *Du Bois review: social science research on race* **8**, 143 (2011).
15. C. P. Jones, Toward the science and practice of anti-racism: launching a National Campaign against Racism. *Ethnicity & disease* **28**, 231 (2018).
16. M. Luke, K. M. Goodrich, Working with family, friends, and allies of LBGT youth. *Journal for Social Action in Counseling & Psychology* **7**, 63-83 (2015).
17. D. R. Williams, J. A. Lawrence, B. A. Davis, Racism and health: evidence and needed research. *Annual review of public health* **40**, 105-125 (2019).
18. A. Montgomery, Reappearance of the public: Placemaking, minoritization and resistance in Detroit. *International Journal of Urban and Regional Research* **40**, 776-799 (2016).
19. L. Kcomt, Profound health-care discrimination experienced by transgender people: rapid systematic review. *Social work in health care* **58**, 201-219 (2019).

20. J. Shelton *et al.*, Homelessness and housing experiences among LGBTQ young adults in seven US cities. *Cityscape* **20**, 9-34 (2018).
21. A. V. Diez Roux, Investigating neighborhood and area effects on health. *American journal of public health* **91**, 1783-1789 (2001).
22. A. S. Felix *et al.*, Stress, resilience, and cardiovascular disease risk among black women: results from the Women's Health Initiative. *Circulation: Cardiovascular Quality and Outcomes* **12**, e005284 (2019).
23. M. A. Grandner, N. J. Williams, K. L. Knutson, D. Roberts, G. Jean-Louis, Sleep disparity, race/ethnicity, and socioeconomic position. *Sleep medicine* **18**, 7-18 (2016).
24. D. R. Williams, J. A. Lawrence, B. A. Davis, C. Vu, Understanding how discrimination can affect health. *Health services research* **54**, 1374-1388 (2019).
25. P. D. Gluckman, M. A. Hanson, C. Cooper, K. L. Thornburg, Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine* **359**, 61-73 (2008).
26. C. N. Hales, D. J. Barker, The thrifty phenotype hypothesis: Type 2 diabetes. *British medical bulletin* **60**, 5-20 (2001).
27. L. S. Adair, A. M. Prentice, A critical evaluation of the fetal origins hypothesis and its implications for developing countries. *The Journal of nutrition* **134**, 191-193 (2004).
28. A. D. Richman, Concurrent social disadvantages and chronic inflammation: the intersection of race and ethnicity, gender, and socioeconomic status. *Journal of racial and ethnic health disparities* **5**, 787-797 (2018).
29. R. L. Simons *et al.*, Discrimination, segregation, and chronic inflammation: Testing the weathering explanation for the poor health of Black Americans. *Developmental psychology* **54**, 1993 (2018).
30. K. Korpela *et al.*, Selective maternal seeding and environment shape the human gut microbiome. *Genome Res* **28**, 561-568 (2018).
31. D. Rothschild *et al.*, Environment dominates over host genetics in shaping human gut microbiota. *Nat* **555**, 210-215 (2018).
32. S. J. Song *et al.*, Cohabiting family members share microbiota with one another and with their dogs. *eLife* **2**, e00458 (2013).
33. A. Spor, O. Koren, R. E. Ley, Unravelling the effects of the environment and host genotype on the gut microbiome. *Nat Rev* **9**, 279-290 (2011).
34. L. Mancabelli *et al.*, Meta-analysis of the human gut microbiome from urbanized and pre-agricultural populations. *Environ Microbiol* **19**, 1379-1390 (2017).
35. K. Stagaman *et al.*, Market integration predicts human gut microbiome attributes across a gradient of economic development. *Msystems* **3**, e00122-00117 (2018).
36. Z. Al Nabhani, G. Eberl, Imprinting of the immune system by the microbiota early in life. *Mucosal Immunology*, 183-189 (2020).
37. J. F. Cryan *et al.*, The microbiota-gut-brain axis. *Physiol Rev* **99**, 1877-2013 (2019).
38. G. N. Pronovost, E. Y. Hsiao, Perinatal interactions between the microbiome, immunity, and neurodevelopment. *Immunity* **50**, 18-36 (2019).
39. S. Sanna *et al.*, Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. *Nat Genet* **51**, 600-605 (2019).

40. J. U. Scher, R. R. Nayak, C. Ubeda, P. J. Turnbaugh, S. B. Abramson, Pharmacomicrobiomics in inflammatory arthritis: gut microbiome as modulator of therapeutic response. *Nature Reviews Rheumatology*, 1-11 (2020).
41. A. Visconti *et al.*, Interplay between the human gut microbiome and host metabolism. *Nat Comm* **10**, 1-10 (2019).
42. A. Leshem, T. Liwinski, E. Elinav, Immune-microbiota interplay and colonization resistance in infection. *Molecular Cell* (2020).
43. M. B. Azad *et al.*, Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study. *Eur Respir J* **49** (2017).
44. J. A. Foster, K. A. McVey Neufeld, Gut-brain axis: How the microbiome influences anxiety and depression. *Cell* **36**, 305-312 (2013).
45. A. Giongo *et al.*, Toward defining the autoimmune microbiome for type 1 diabetes. *ISME J* **5**, 82-91 (2011).
46. J. Halfvarson *et al.*, Dynamics of the human gut microbiome in inflammatory bowel disease. *Nature microbiology* **2**, 17004 (2017).
47. S. Jangi *et al.*, Alterations of the human gut microbiome in multiple sclerosis. *Nat Comm* **7**, 12015 (2016).
48. R. A. Koeth *et al.*, Intestinal microbiota metabolism ofL-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature Medicine* **19**, 576-585 (2013).
49. R. Krajmalnik-Brown, C. Lozupone, D. W. Kang, J. B. Adams, Gut bacteria in children with autism spectrum disorders: Challenges and promise of studying how a complex community influences a complex disease. *Microb Ecol* **26** (2015).
50. N. Larsen *et al.*, Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* **5**, e9085 (2010).
51. P. J. Turnbaugh *et al.*, An obesity-associated gut microbiome with increased capacity for energy harvest. *Nat* **444**, 1027-1031 (2006).
52. A. Keshavarzian *et al.*, Colonic bacterial composition in Parkinson's disease. *Movement Disorders* **30**, 1351-1360 (2015).
53. M. C. Arrieta *et al.*, Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* **7**, 307ra152 (2015).
54. E. Dikongué, L. Ségurel, Latitude as a co-driver of human gut microbial diversity? *BioEssays* **39**, 1600145 (2017).
55. M.-C. Arrieta *et al.*, Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* **7**, 307ra152-307ra152 (2015).
56. R. C. Bowyer *et al.*, Socioeconomic status and the gut microbiome: a TwinsUK cohort study. *Microorganisms* **7**, 17 (2019).
57. C. W. Chong *et al.*, Effect of ethnicity and socioeconomic variation to the gut microbiota composition among pre-adolescent in Malaysia. *Scientific reports* **5**, 13338 (2015).
58. G. E. Miller *et al.*, Lower neighborhood socioeconomic status associated with reduced diversity of the colonic microbiota in healthy adults. *PLoS One* **11**, e0148952 (2016).
59. A. W. Brooks, S. Priya, R. Blekhman, S. R. Bordenstein, Gut microbiota diversity across ethnicities in the United States. *PLoS Biol* **16** (2018).

60. R. C. Kaplan *et al.*, Gut microbiome composition in the Hispanic Community Health Study/Study of Latinos is shaped by geographic relocation, environmental factors, and obesity. *Genome Biol* **20**, 219 (2019).
61. K. Sankaranarayanan *et al.*, Gut microbiome diversity among Cheyenne and Arapaho individuals from western Oklahoma. *Current Biology* **25**, 3161-3169 (2015).
62. J. D. Galley, M. Bailey, C. K. Dush, S. Schoppe-Sullivan, L. M. Christian, Maternal obesity is associated with alterations in the gut microbiome in toddlers. *PLoS One* **9**, e113026 (2014).
63. J. B. Dowd, A. Renson, "Under the Skin" and into the Gut: Social Epidemiology of the Microbiome. *Current epidemiology reports* **5**, 432-441 (2018).
64. K. Findley, D. R. Williams, E. A. Grice, V. L. Bonham, Health disparities and the microbiome. *Trends in microbiology* **24**, 847-850 (2016).
65. E. Rackaityte *et al.*, Viable bacterial colonization is highly limited in the human intestine in utero. *Nature Medicine*, 1-9 (2020).
66. J. E. Koenig *et al.*, Succession of microbial consortia in the developing infant gut microbiome. *PNAS* **108**, 4578-4585 (2011).
67. K. M. Aagaard *et al.*, The placenta harbors a unique microbiome. *Sci Transl Med* **6**, 237ra265 (2014).
68. C. Mitchell *et al.*, Delivery mode impacts newborn gut colonization efficiency. *bioRxiv* (2020).
69. P. Ferretti *et al.*, Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. *Cell host & microbe* **24**, 133-145. e135 (2018).
70. M. Yassour *et al.*, Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Sci Transl Med* **8**, 343ra381-343ra381 (2016).
71. M. G. Dominguez-Bello *et al.*, Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats. *PNAS* **107**, 11971-11975 (2010).
72. Y. Shao *et al.*, Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. *Nat* **574**, 117-121 (2019).
73. M. B. Azad *et al.*, Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology* **123**, 983-993 (2016).
74. S. Tamburini, N. Shen, H. C. Wu, J. C. Clemente, The microbiome in early life: implications for health outcomes. *Nature medicine* **22**, 713 (2016).
75. C. Milani *et al.*, The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota. *Microbiol. Mol. Biol. Rev.* **81**, e00036-00017 (2017).
76. A. M. Zivkovic, J. B. German, C. B. Lebrilla, D. A. Mills, Human milk glycobiome and its impact on the infant gastrointestinal microbiota. *PNAS* **108**, 4653-4658 (2011).
77. S. Moossavi *et al.*, Composition and variation of the human milk microbiota are influenced by maternal and early-life factors. *Cell host & microbe* **25**, 324-335. e324 (2019).

78. G. Oikonomou *et al.*, Milk microbiota: what are we exactly talking about? *Frontiers in microbiology* **11**, 60 (2020).
79. M. B. Azad *et al.*, Human milk oligosaccharide concentrations are associated with multiple fixed and modifiable maternal characteristics, environmental factors, and feeding practices. *The Journal of nutrition* **148**, 1733-1742 (2018).
80. L. Bode, "Human milk oligosaccharides: structure and functions" in Milk, Mucosal Immunity, and the Microbiome: Impact on the Neonate. (Karger Publishers, 2020), vol. 94, pp. 115-123.
81. N. A. Bokulich *et al.*, Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med* **8**, 343ra382 (2016).
82. C. J. Stewart *et al.*, Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nat* **562**, 583-588 (2018).
83. J. D. Forbes *et al.*, Association of exposure to formula in the hospital and subsequent infant feeding practices with gut microbiota and risk of overweight in the first year of life. *JAMA pediatrics* **172**, e181161-e181161 (2018).
84. H. Neuman, J. W. Debelius, R. Knight, O. Koren, Microbial endocrinology: The interplay between the microbiota and the endocrine system. *FEMS Microbiol Rev* 10.1093/femsre/fuu010 (2015).
85. M. Bailey, C. L. Coe, Maternal separation disrupts the integrity of the intestingal micoflora in infant rhesus monkeys. *Dev Psychobiol* **35**, 146-155 (1999).
86. K. Suzuki, R. Harasawa, Y. Yoshitake, T. Mitsuoka, Effect of crowding and heat stress on intestinal flora, body weight gain, and feed efficiency of growing rats and chicks. *Nippon Juigaku Zasshi* **45** (1983).
87. C. L. Meehan *et al.*, Social networks, cooperative breeding, and the human milk microbiome. *Am J Hum Biol* **30**, e23131 (2018).
88. M. H. Tun *et al.*, Postnatal exposure to household disinfectants, infant gut microbiota and subsequent risk of overweight in children. *CMAJ* **190**, E1097-E1107 (2018).
89. T. Yatsunenko *et al.*, Human gut microbiome viewed across age and geography. *Nat* **486**, 222-227 (2012).
90. L. A. David *et al.*, Diet rapidly and reproducibly alters the human gut microbiome. *Nat* **505**, 559-566 (2014).
91. I. Martinez *et al.*, The gut microbiota of rural Papua New Guineans: Composition, diversity patterns, and ecological processes. *Cell Reports* **11**, 527-538 (2015).
92. A. J. Obregon-Tito *et al.*, Subsistence strategies in traditional societies distinguish gut microbiomes. *Nat Comm* **6**, 6505 (2015).
93. S. L. Schnorr *et al.*, Gut microbiome of Hadza hunter-gatherers. *Nat Comm* **5**, 3654 (2014).
94. C. De Filippo *et al.*, Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *PNAS* **107**, 14691-14696 (2010).
95. T. L. Carson *et al.*, Associations Between Race, Perceived Psychological Stress, and the Gut Microbiota in a Sample of Generally Healthy Black and White Women: A Pilot Study on the Role of Race and Perceived Psychological Stress. *Psychosomatic medicine* **80**, 640-648 (2018).
96. J. Peter *et al.*, A microbial signature of psychological distress in irritable bowel syndrome. *Psychosomatic medicine* 10.1097/PSY.0000000000000630 (2018).

97. M. T. Bailey *et al.*, Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain, behavior, and immunity* **25**, 397-407 (2011).
98. A. Bharwani *et al.*, Structural & functional consequences of chronic psychosocial stress on the microbiome & host. *Psychoneuroendocrinology* **63**, 217-227 (2016).
99. J. D. Galley, A. R. Mackos, V. A. varaljay, M. T. Bailey, Stressor exposure has prolonged effects on colonic microbial community structure in Citrobacter rodentium-challenged mice. *Scientific reports* **7:45012** (2017).
100. J. D. Galley *et al.*, The structures of the colonic mucosa-associated and luminal microbial communities are distinct and differentially affected by a prolonged murine stressor. *Gut microbes* **5**, 748-760 (2014).
101. A. Lokmer *et al.*, Response of the human gut and saliva microbiome to urbanization in cameroon. *Scientific reports* **10**, 1-15 (2020).
102. G. Falony *et al.*, Population-level analysis of gut microbiome variation. *Science* **352**, 560-564 (2016).
103. R. Blekhman *et al.*, Host genetic variation impacts microbiome composition across human body sites. *Genome Biol* **16** (2015).
104. E. R. Davenport *et al.*, Genome-wide association studies of the human gut microbiota. *PLoS One* **10**, e0140301 (2015).
105. W. Turpin *et al.*, Association of host genome with intestinal microbial composition in a large healthy cohort. *Nat Genet* **48**, 1413 (2016).
106. M. J. Bonder *et al.*, The effect of host genetics on the gut microbiome. *Nat Genet* **48**, 1407-1412 (2016).
107. H. Xie *et al.*, Shotgun metagenomics of 250 adult twins reveals genetic and environmental impacts on the gut microbiome. *Cell systems* **3**, 572-584. e573 (2016).
108. J. K. Goodrich *et al.*, Human genetics shape the gut microbiome. *Cell* **159** (2014).
109. T. Olszak *et al.*, Microbial exposure during early life has persistent effects on natural killer T cell function. *Science* **336**, 489-493 (2012).
110. J. A. Griffiths, S. K. Mazmanian, Emerging evidence linking the gut microbiome to neurologic disorders. *Genome medicine* **10**, 98 (2018).
111. R. A. Dimmitt *et al.*, The role of postnatal acquisition of the intestinal microbiome in the early development of immune function. *Journal of pediatric gastroenterology and nutrition* **51**, 262 (2010).
112. J. D. Planer *et al.*, Development of the gut microbiota and mucosal IgA responses in twins and gnotobiotic mice. *Nat* **534**, 263-266 (2016).
113. N. Sudo *et al.*, Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol* **558**, 263-275 (2004).
114. S. K. Mazmanian, C. H. Liu, A. O. Tzianabos, D. L. Kasper, An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* **122**, 107-118 (2005).
115. L. M. Cox *et al.*, Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* **158**, 705-721 (2014).
116. E. D. Sonnenburg *et al.*, Diet-induced extinctions in the gut microbiota compound over generations. *Nat* **529**, 212-215 (2016).

117. A. F. Schulfer *et al.*, The impact of early-life sub-therapeutic antibiotic treatment (STAT) on excessive weight is robust despite transfer of intestinal microbes. *The ISME journal* **13**, 1280-1292 (2019).
118. W. H. O. United Nations Children's Fund , International Bank for Reconstruction, D. T. W. Bank, Levels and trends in child malnutrition: Key findings of the 2019 edition of the joint child malnutrition estimates. (2019).
119. M.-E. N. Investigators, Childhood stunting in relation to the pre-and postnatal environment during the first 2 years of life: The MAL-ED longitudinal birth cohort study. *PLoS medicine* **14** (2017).
120. K. G. Dewey, K. Begum, Long-term consequences of stunting in early life. *Maternal & child nutrition* **7**, 5-18 (2011).
121. S. Subramanian *et al.*, Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nat* **510**, 417-421 (2014).
122. C. Bommer, S. Vollmer, S. Subramanian, How socioeconomic status moderates the stunting-age relationship in low-income and middle-income countries. *BMJ global health* **4**, e001175 (2019).
123. R. L. Guerrant, M. D. DeBoer, S. R. Moore, R. J. Scharf, A. A. Lima, The impoverished gut—a triple burden of diarrhoea, stunting and chronic disease. *Nature reviews Gastroenterology & hepatology* **10**, 220 (2013).
124. S. Becker-Dreps *et al.*, Gut microbiome composition in young Nicaraguan children during diarrhea episodes and recovery. *The American journal of tropical medicine and hygiene* **93**, 1187-1193 (2015).
125. L. V. Blanton *et al.*, Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. *Science* **351**, aad3311 (2016).
126. D. M. Dinh *et al.*, Longitudinal analysis of the intestinal microbiota in persistently stunted young children in South India. *PLoS One* **11** (2016).
127. S. Rouhani *et al.*, Gut microbiota features associated with Campylobacter burden and postnatal linear growth deficits in a Peruvian birth cohort. *Clinical Infectious Diseases* (2019).
128. M. I. Smith *et al.*, Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. *Science* **339**, 548-554 (2013).
129. P. Vonaesch *et al.*, Stunted childhood growth is associated with decompartmentalization of the gastrointestinal tract and overgrowth of oropharyngeal taxa. *Proceedings of the National Academy of Sciences* **115**, E8489-E8498 (2018).
130. J. L. Gehrig *et al.*, Effects of microbiota-directed foods in gnotobiotic animals and undernourished children. *Science* **365**, eaau4732 (2019).
131. M. Schwarzer *et al.*, Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition. *Science* **351**, 854-857 (2016).
132. T. Cullen *et al.*, Antimicrobial peptide resistance mediates resilience of prominent gut commensals during inflammation. *Science* **347**, 170-175 (2015).
133. K. P. Pavlick *et al.*, Role of reactive metabolites of oxygen and nitrogen in inflammatory bowel disease. *Free Radical Biology and Medicine* **33**, 311-322 (2002).
134. L. Rigottier-Gois, Dysbiosis in inflammatory bowel diseases: the oxygen hypothesis. *The ISME journal* **7**, 1256-1261 (2013).

135. D. J. Corsi, I. Mejía-Guevara, S. Subramanian, Risk factors for chronic undernutrition among children in India: Estimating relative importance, population attributable risk and fractions. *Social Science & Medicine* **157**, 165-185 (2016).
136. B. J. Akombi *et al.*, Stunting, wasting and underweight in sub-Saharan Africa: a systematic review. *International journal of environmental research and public health* **14**, 863 (2017).
137. T. D. Hinson, A. C. Skinner, K. H. Lich, D. L. Spatz, Factors that influence breastfeeding initiation among African American women. *Journal of Obstetric, Gynecologic & Neonatal Nursing* **47**, 290-300 (2018).
138. M. G. Craft-Blacksheare, Lessons learned from the crisis in flint, Michigan regarding the effects of contaminated water on maternal and child health. *Journal of Obstetric, Gynecologic & Neonatal Nursing* **46**, 258-266 (2017).
139. E. W. Kimani-Murage *et al.*, Evidence of a double burden of malnutrition in urban poor settings in Nairobi, Kenya. *PLoS One* **10** (2015).
140. M. K. Mirzaei *et al.*, Bacteriophages isolated from stunted children can regulate gut bacterial communities in an age-specific manner. *Cell host & microbe* **27**, 199-212. e195 (2020).
141. M. Blüher, Obesity: global epidemiology and pathogenesis. *Nature Reviews Endocrinology* **15**, 288 (2019).
142. B. M. Popkin, L. S. Adair, S. W. Ng, Global nutrition transition and the pandemic of obesity in developing countries. *Nutr Rev* **70**, 3-21 (2012).
143. P. H. Bryant, A. Hess, P. G. Bowen, Social determinants of health related to obesity. *The Journal for Nurse Practitioners* **11**, 220-225 (2015).
144. C. M. Hales, M. D. Carroll, C. D. Fryar, C. L. Ogden, Prevalence of obesity and severe obesity among adults: United States, 2017–2018. (2020).
145. R. Blekhman *et al.*, Comparative metabolomics in primates reveals the effects of diet and gene regulatory variation on metabolic divergence. *Scientific reports* **4**, 5809 (2014).
146. P. D. Cani *et al.*, Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **56**, 1761-1772 (2007).
147. B. Chassaing, R. E. Ley, A. T. Gewirtz, Intestinal epithelial cell toll-like receptor 5 regulates the intestinal microbiota to prevent low-grade inflammation and metabolic syndrome in mice. *Gastroenterol* **147**, 1363-1377. e1317 (2014).
148. S. A. Joyce, C. G. Gahan, Bile acid modifications at the microbe-host interface: potential for nutraceutical and pharmaceutical interventions in host health. *Annual review of food science and technology* **7**, 313-333 (2016).
149. I. Kimura *et al.*, Maternal gut microbiota in pregnancy influences offspring metabolic phenotype in mice. *Science* **367**, eaaw8429 (2020).
150. K. M. Utzschneider, M. Kratz, C. J. Damman, M. Hullarg, Mechanisms linking the gut microbiome and glucose metabolism. *The Journal of Clinical Endocrinology & Metabolism* **101**, 1445-1454 (2016).
151. R. E. Ley, P. J. Turnbaugh, S. Klein, J. I. Gordon, Human gut microbes associated with obesity. *Nat* **444**, 1022-1023 (2006).
152. V. K. Ridaura *et al.*, Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* **341**, 1069-1070 (2013).

153. A. Schwiertz *et al.*, Microbiota and SCFA in lean and overweight healthy subjects. *Obesity* **18**, 190-195 (2010).
154. J. Blustein *et al.*, Association of caesarean delivery with child adiposity from age 6 weeks to 15 years. *International Journal of Obesity* **37**, 900-906 (2013).
155. F. Magne, A. Puchi Silva, B. Carvajal, M. Gotteland, The elevated rate of cesarean section and its contribution to non-communicable chronic diseases in Latin America: the growing involvement of the microbiota. *Frontiers in pediatrics* **5**, 192 (2017).
156. H. M. Timmerman *et al.*, Intestinal colonisation patterns in breastfed and formula-fed infants during the first 12 weeks of life reveal sequential microbiota signatures. *Scientific reports* **7**, 8327 (2017).
157. N. C. Nickel *et al.*, Have we left some behind? Trends in socio-economic inequalities in breastfeeding initiation: a population-based epidemiological surveillance study. *Canadian Journal of Public Health* **105**, e362-e368 (2014).
158. J. K. Edmonds, R. Yehezkel, X. Liao, T. A. M. Simas, Racial and ethnic differences in primary, unscheduled cesarean deliveries among low-risk primiparous women at an academic medical center: a retrospective cohort study. *BMC pregnancy and childbirth* **13**, 168 (2013).
159. J. E. Bisanz, V. Upadhyay, J. A. Turnbaugh, K. Ly, P. Turnbaugh, Diet induces reproducible alterations in the mouse and human gut microbiome. *Available at SSRN 3330558* (2019).
160. P. Jia, H. Xue, X. Cheng, Y. Wang, Effects of school neighborhood food environments on childhood obesity at multiple scales: a longitudinal kindergarten cohort study in the USA. *BMC medicine* **17**, 99 (2019).
161. J. L. Zagorsky, P. K. Smith, The association between socioeconomic status and adult fast-food consumption in the US. *Economics & Human Biology* **27**, 12-25 (2017).
162. L. M. Cox, M. J. Blaser, Pathways in microbe-induced obesity. *Cell Metab* **17**, 883-894 (2013).
163. L. Trasande *et al.*, Infant antibiotic exposures and early life body mass. *International Journal of Obesity* **37**, 16-23 (2013).
164. T. Ajslev, C. Andersen, M. Gamborg, T. Sørensen, T. Jess, Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *International journal of obesity* **35**, 522-529 (2011).
165. C. Volpi, F. Shehadeh, E. Mylonakis, Correlation of antimicrobial prescription rate and county income in medicare part D. *Medicine* **98** (2019).
166. K. I. Proper *et al.*, The relationship between shift work and metabolic risk factors: a systematic review of longitudinal studies. *American Journal of Preventive Medicine* **50**, e147-e157 (2016).
167. R. Voigt, C. Forsyth, S. Green, P. Engen, A. Keshavarzian, "Circadian rhythm and the gut microbiome" in International review of neurobiology. (Elsevier, 2016), vol. 131, pp. 193-205.
168. R. M. Voigt *et al.*, Circadian disorganization alters intestinal microbiota. *PLoS One* **9**, e97500 (2014).
169. F. Bishehsari, A. Keshavarzian, Microbes help to track time. *Science* **365**, 1379-1380 (2019).

170. V. Leone *et al.*, Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. *Cell Host Microbe* **17**, 681-689 (2015).
171. C. A. Thaiss *et al.*, Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* **159**, 514-529 (2014).
172. C. Benedict *et al.*, Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivation in normal-weight young individuals. *Molecular metabolism* **5**, 1175-1186 (2016).
173. V. A. Poroyko *et al.*, Chronic Sleep Disruption Alters Gut Microbiota, Induces Systemic and Adipose Tissue Inflammation and Insulin Resistance in Mice. *Scientific reports* **6**, 35405 (2016).
174. S. L. Zhang *et al.*, Human and rat gut microbiome composition is maintained following sleep restriction. *Proc Natl Acad Sci U S A* **114**, E1564-E1571 (2017).
175. S. Jehan *et al.*, Sleep health disparity: the putative role of race, ethnicity and socioeconomic status. *Sleep medicine and disorders: international journal* **2**, 127 (2018).
176. A. D. Laposky, E. Van Cauter, A. V. Diez-Roux, Reducing health disparities: the role of sleep deficiency and sleep disorders. *Sleep medicine* **18**, 3-6 (2016).
177. J. D. Galley, M. Bailey, C. K. Dush, S. Schoppe-Sullivan, L. M. Christian, Maternal obesity is associated with alterations in the gut microbiome in toddlers. *PLoS One* **9** (2014).
178. N. T. Mueller *et al.*, Birth mode-dependent association between pre-pregnancy maternal weight status and the neonatal intestinal microbiome. *Scientific Reports* **6**, 23133 (2016).
179. H. M. Tun *et al.*, Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring. *JAMA pediatrics* **172**, 368-377 (2018).
180. G. A. Network (2018) Global Asthma Report 2018.
181. S. S. Braman, The global burden of asthma. *Chest* **130**, 4S-12S (2006).
182. G. Ferrante, S. La Grutta, The burden of pediatric asthma. *Frontiers in pediatrics* **6**, 186 (2018).
183. G. W. Wong, C. M. Chow, Childhood asthma epidemiology: insights from comparative studies of rural and urban populations. *Pediatr Pulmonol* **43**, 107-116 (2008).
184. S. Timm *et al.*, The Urban-Rural Gradient In Asthma: A Population-Based Study in Northern Europe. *Int J Environ Res Public Health* **13** (2015).
185. M. M. Stein *et al.*, Innate immunity and asthma risk in Amish and Hutterite farm children. *New England journal of medicine* **375**, 411-421 (2016).
186. P. J. Cooper *et al.*, Hygiene, atopy and wheeze-eczema-rhinitis symptoms in schoolchildren from urban and rural Ecuador. *Thorax* **69**, 232-239 (2014).
187. K. Negele *et al.*, Mode of delivery and development of atopic disease during the first 2 years of life. *Pediatr Allergy Immunol* **15**, 48-54 (2004).
188. S. Thavagnanam, J. Fleming, A. Bromley, M. D. Shields, C. R. Cardwell, A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy* **38**, 629-633 (2008).
189. M. C. Arrieta, L. T. Stiemsma, N. Amenyogbe, E. M. Brown, B. Finlay, The intestinal microbiome in early life: health and disease. *Front Immunol* **5**, 427 (2014).

190. A. Klopp *et al.*, Modes of Infant Feeding and the Risk of Childhood Asthma: A Prospective Birth Cohort Study. *J Pediatr* **190**, 192-199 e192 (2017).
191. K. Loewen, B. Monchka, S. M. Mahmud, G. t Jong, M. B. Azad, Prenatal antibiotic exposure and childhood asthma: a population-based study. *Eur Respir J* **52** (2018).
192. S. L. Russell *et al.*, Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep* **13**, 440-447 (2012).
193. D. W. Denning, B. R. O'Driscoll, C. M. Hogaboam, P. Bowyer, R. M. Niven, The link between fungi and severe asthma: a summary of the evidence. *Eur Respir J* **27**, 615-626 (2006).
194. R. T. Stein *et al.*, Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* **354**, 541-545 (1999).
195. S. L. Bridgman, A. L. Kozyrskyj, J. A. Scott, A. B. Becker, M. B. Azad, Gut microbiota and allergic disease in children. *Ann Allergy Asthma Immunol* **116**, 99-105 (2016).
196. M. Hilty *et al.*, Disordered microbial communities in asthmatic airways. *PLoS One* **5**, e8578 (2010).
197. P. R. Marri, D. A. Stern, A. L. Wright, D. Billheimer, F. D. Martinez, Asthma-associated differences in microbial composition of induced sputum. *J Allergy Clin Immunol* **131**, 346-352 e341-343 (2013).
198. Q. Zhang *et al.*, Airway Microbiota in Severe Asthma and Relationship to Asthma Severity and Phenotypes. *PLoS One* **11**, e0152724 (2016).
199. J. Stokholm *et al.*, Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun* **9**, 141 (2018).
200. M. C. Arrieta *et al.*, Associations between infant fungal and bacterial dysbiosis and childhood atopic wheeze in a nonindustrialized setting. *J Allergy Clin Immunol* **142**, 424-434 e410 (2018).
201. E. von Mutius, K. Radon, Living on a farm: impact on asthma induction and clinical course. *Immunol Allergy Clin North Am* **28**, 631-647, ix-x (2008).
202. B. J. Stoll *et al.*, Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* **126**, 443-456 (2010).
203. F. A. Carter, M. E. Msall, Long-term functioning and participation across the life course for preterm neonatal intensive care unit graduates. *Clinics in perinatology* **45**, 501-527 (2018).
204. F. A. Carter, M. E. Msall, Health disparities and child development after prematurity. *Pediatric annals* **46**, e360-e364 (2017).
205. H. S. Wong, P. Edwards, Nature or nurture: a systematic review of the effect of socio-economic status on the developmental and cognitive outcomes of children born preterm. *Maternal and child health journal* **17**, 1689-1700 (2013).
206. A. I. Patrianakos-Hoobler *et al.*, Predicting school readiness from neurodevelopmental assessments at age 2 years after respiratory distress syndrome in infants born preterm. *Developmental Medicine & Child Neurology* **52**, 379-385 (2010).
207. M. G. Welch *et al.*, Family nurture intervention in the neonatal intensive care unit improves social-relatedness, attention, and neurodevelopment of preterm infants at 18 months in a randomized controlled trial. *Journal of Child Psychology and Psychiatry* **56**, 1202-1211 (2015).

208. L. Lu *et al.*, Transcriptional modulation of intestinal innate defense/inflammation genes by preterm infant microbiota in a humanized gnotobiotic mouse model. *PLoS One* **10**, e0124504 (2015).
209. J. W. van der Burg *et al.*, The role of systemic inflammation linking maternal BMI to neurodevelopment in children. *Pediatr Res* **79**, 3-12 (2016).
210. K. Jarlestedt, A. S. Naylor, J. Dean, H. Hagberg, C. Mallard, Decreased survival of newborn neurons in the dorsal hippocampus after neonatal LPS exposure in mice. *Neuroscience* **253**, 21-28 (2013).
211. P. L. Smith, H. Hagberg, A. S. Naylor, C. Mallard, Neonatal peripheral immune challenge activates microglia and inhibits neurogenesis in the developing murine hippocampus. *Developmental neuroscience* **36**, 119-131 (2014).
212. A. L. Carlson *et al.*, Infant Gut Microbiome Associated With Cognitive Development. *Biol Psychiatry* 10.1016/j.biopsych.2017.06.021 (2017).
213. P. A. Brennan *et al.*, Protocol for the Emory University African American maternal stress and infant gut microbiome cohort study. *BMC pediatrics* **19**, 246 (2019).
214. D. Vigo, G. Thornicroft, R. Atun, Estimating the true global burden of mental illness. *The Lancet Psychiatry* **3**, 171-178 (2016).
215. W. H. Organization (2017) Depression and other common mental disorders: global health estimates. (World Health Organization).
216. V. Lorant *et al.*, Socioeconomic inequalities in depression: a meta-analysis. *American journal of epidemiology* **157**, 98-112 (2003).
217. M. J. Zvolensky, L. Garey, J. Bakhshaie (2017) Disparities in anxiety and its disorders. (Elsevier).
218. S. Wallace, J. Nazroo, L. Bécares, Cumulative effect of racial discrimination on the mental health of ethnic minorities in the United Kingdom. *American Journal of Public Health* **106**, 1294-1300 (2016).
219. J. Kates, U. Ranji, A. Beamesderfer, A. Salganicoff, L. Dawson, Health and access to care and coverage for Lesbian, Gay, Bisexual and Transgender (LGBT) individuals in the US. (2015).
220. A. Abrams, M. Goyal, G. Badolato (2019) Racial disparities in pediatric mental health-related emergency department visits: a five-year multi-institutional study. (Am Acad Pediatrics).
221. A. H. Miller, C. L. Raison, The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature reviews. Immunology* **16**, 22-34 (2016).
222. J. Schinka, R. Busch, N. Robichaux-Keene, A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. *Molecular psychiatry* **9**, 197-202 (2004).
223. S. E. Quirk *et al.*, The association between diet quality, dietary patterns and depression in adults: a systematic review. *BMC psychiatry* **13**, 175 (2013).
224. H. Van Praag, Can stress cause depression? *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **28**, 891-907 (2004).
225. C. Hammen, P. A. Brennan, J. H. Shih, Family discord and stress predictors of depression and other disorders in adolescent children of depressed and nondepressed women. *Journal of the American Academy of Child & Adolescent Psychiatry* **43**, 994-1002 (2004).

226. D. Gibson-Smith *et al.*, Association of food groups with depression and anxiety disorders. *European journal of nutrition* **59**, 767-778 (2020).
227. H. Jiang *et al.*, Altered fecal microbiota composition in patients with major depressive disorder. *Brain, Behav, Immun* **48**, 186-194 (2015).
228. M. Yu *et al.*, Variations in gut microbiota and fecal metabolic phenotype associated with depression by 16S rRNA gene sequencing and LC/MS-based metabolomics. *Journal of pharmaceutical and biomedical analysis* **138**, 231-239 (2017).
229. J. R. Kelly *et al.*, Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. *Journal of psychiatric research* **82**, 109-118 (2016).
230. A. Burokas *et al.*, Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. *Biological psychiatry* **82**, 472-487 (2017).
231. A. Kazemi, A. A. Noorbala, K. Azam, M. H. Eskandari, K. Djafarian, Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. *Clin Nutr* **38**, 522-528 (2019).
232. M. Messaoudi *et al.*, Assessment of psychotropic-like properties of a probiotic fomulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. *Br J Nutr* **105**, 755-764 (2010).
233. R. Huo *et al.*, Microbiota Modulate Anxiety-Like Behavior and Endocrine Abnormalities in Hypothalamic-Pituitary-Adrenal Axis. *Frontiers in cellular and infection microbiology* **7**, 489 (2017).
234. S. M. O'Mahony, G. Clarke, Y. Borre, T. Dinan, J. Cryan, Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behavioural brain research* **277**, 32-48 (2015).
235. M. Vodicka *et al.*, Microbiota affects the expression of genes involved in HPA axis regulation and local metabolism of glucocorticoids in chronic psychosocial stress. *Brain, behavior, and immunity* **73**, 615-624 (2018).
236. J. M. Yano *et al.*, Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* **161**, 264-276 (2015).
237. J. A. Bravo *et al.*, Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences of the United States of America* **108**, 16050-16055 (2011).
238. P. Forsythe, J. Bienenstock, W. A. Kunze, Vagal pathways for microbiome-brain-gut axis communication. *Advances in experimental medicine and biology* **817**, 115-133 (2014).
239. S. Dash, G. Clarke, M. Berk, F. N. Jacka, The gut microbiome and diet in psychiatry: focus on depression. *Current opinion in psychiatry* **28**, 1-6 (2015).
240. J. R. Kelly *et al.*, Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Frontiers in cellular neuroscience* **9**, 392 (2015).
241. M. Maes, M. Kubera, J.-C. Leunis, M. Berk, Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. *Journal of affective disorders* **141**, 55-62 (2012).

242. A. Slyepchenko *et al.*, Intestinal dysbiosis, gut hyperpermeability and bacterial translocation: missing links between depression, obesity and type 2 diabetes. *Current pharmaceutical design* **22**, 6087-6106 (2016).
243. T. L. Gur *et al.*, Prenatal stress affects placental cytokines and neurotrophins, commensal microbes, and anxiety-like behavior in adult female offspring. *Brain, behavior, and immunity* 10.1016/j.bbi.2016.12.021 (2016).
244. E. Jasarevic, C. D. Howard, A. M. Misic, D. P. Beiting, T. L. Bale, Stress during pregnancy alters temporal and spatial dynamics of the maternal and offspring microbiome in a sex-specific manner. *Scientific reports* **7**, 44182 (2017).
245. T. L. Gur *et al.*, Prenatal stress disrupts social behavior, cortical neurobiology and commensal microbes in adult male offspring. *Behavioural brain research* 10.1016/j.bbr.2018.06.025 (2018).
246. M. W. Hooper, A. M. Nápoles, E. J. Pérez-Stable, COVID-19 and racial/ethnic disparities. *Jama* (2020).
247. A. van Dorn, R. E. Cooney, M. L. Sabin, COVID-19 exacerbating inequalities in the US. *Lancet (London, England)* **395**, 1243 (2020).
248. M. Chowkwanyun, A. L. Reed Jr, Racial health disparities and Covid-19—caution and context. *New England Journal of Medicine* (2020).
249. J. Lederberg, Infectious history. *Science* **288**, 287-293 (2000).
250. K. H. Antunes *et al.*, Microbiota-derived acetate protects against respiratory syncytial virus infection through a GPR43-type 1 interferon response. *Nat Comm* **10**, 1-17 (2019).
251. K. C. Bradley *et al.*, Microbiota-driven tonic interferon signals in lung stromal cells protect from influenza virus infection. *Cell reports* **28**, 245-256. e244 (2019).
252. J.-M. Cavaillon, Exotoxins and endotoxins: Inducers of inflammatory cytokines. *Toxicon* **149**, 45-53 (2018).
253. Y. Belkaid, T. W. Hand, Role of the microbiota in immunity and inflammation. *Cell* **157**, 121-141 (2014).
254. Y. Yang *et al.*, Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. *MedRxiv* (2020).
255. W. Wang *et al.*, Detection of SARS-CoV-2 in different types of clinical specimens. *Jama* **323**, 1843-1844 (2020).
256. L. Fang, G. Karakiulakis, M. Roth, Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *The Lancet. Respiratory Medicine* **8**, e21 (2020).
257. R. T. Liu, R. F. Walsh, A. E. Sheehan, Prebiotics and probiotics for depression and anxiety: a systematic review and meta-analysis of controlled clinical trials. *Neuroscience & Biobehavioral Reviews* (2019).
258. F. E. Juul *et al.*, Fecal microbiota transplantation for primary Clostridium difficile infection. *New England Journal of Medicine* **378**, 2535-2536 (2018).
259. C. H. Lee *et al.*, Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent Clostridium difficile infection: a randomized clinical trial. *Jama* **315**, 142-149 (2016).
260. J. Suez *et al.*, Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. *Cell* **174**, 1406-1423. e1416 (2018).

261. N. Zmora *et al.*, Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. *Cell* **174**, 1388-1405. e1321 (2018).
262. F. De Filippis *et al.*, Distinct genetic and functional traits of human intestinal Prevotella copri strains are associated with different habitual diets. *Cell host & microbe* **25**, 444-453. e443 (2019).
263. H. A. Swain Ewald, P. W. Ewald, Focus: Ecology and Evolution: Natural Selection, The Microbiome, and Public Health. *The Yale journal of biology and medicine* **91**, 445 (2018).
264. M.-J. Kwak *et al.*, Evolutionary architecture of the infant-adapted group of Bifidobacterium species associated with the probiotic function. *Systematic and applied microbiology* **39**, 429-439 (2016).
265. R. B. Sartor, G. D. Wu, Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. *Gastroenterol* **152**, 327-339. e324 (2017).
266. C. Palmela *et al.*, Adherent-invasive Escherichia coli in inflammatory bowel disease. *Gut* **67**, 574-587 (2018).
267. M. A. Underwood, J. B. German, C. B. Lebrilla, D. A. Mills, Bifidobacterium longum subspecies infantis: champion colonizer of the infant gut. *Pediatric research* **77**, 229-235 (2015).
268. T. Chen *et al.*, Green Tea Polyphenols Modify the Gut Microbiome in db/db Mice as Co-Abundance Groups Correlating with the Blood Glucose Lowering Effect. *Molecular nutrition & food research* **63**, 1801064 (2019).
269. A. P. Galvani, A. S. Parpia, E. M. Foster, B. H. Singer, M. C. Fitzpatrick, Improving the prognosis of health care in the USA. *The Lancet* **395**, 524-533 (2020).
270. C. f. D. Control, Prevention, Racial and socioeconomic disparities in breastfeeding--United States, 2004. *MMWR. Morbidity and mortality weekly report* **55**, 335 (2006).
271. S. Sayres, L. Visentin, Breastfeeding: uncovering barriers and offering solutions. *Curr Opin Pediatr* **30**, 591-596 (2018).
272. N. C. Rollins *et al.*, Why invest, and what it will take to improve breastfeeding practices? *The Lancet* **387**, 491-504 (2016).
273. E. M. Taveras *et al.*, To what extent is the protective effect of breastfeeding on future overweight explained by decreased maternal feeding restriction? *Pediatrics* **118**, 2341-2348 (2006).
274. A. L. Patel *et al.*, Mediators of racial and ethnic disparity in mother's own milk feeding in very low birth weight infants. *Pediatric research* **85**, 662-670 (2019).
275. H. A. S. Ewald, P. W. Ewald, Focus: Ecology and Evolution: Natural Selection, The Microbiome, and Public Health. *The Yale Journal of Biology and Medicine* **91**, 445 (2018).
276. O. O. Balogun *et al.*, Interventions for promoting the initiation of breastfeeding. *Cochrane Database of Systematic Reviews* (2016).
277. S. Haroon, J. K. Das, R. A. Salam, A. Imdad, Z. A. Bhutta, Breastfeeding promotion interventions and breastfeeding practices: a systematic review. *BMC public health* **13**, S20 (2013).
278. M. G. Dominguez-Bello, F. Godoy-Vitorino, R. Knight, M. J. Blaser, Role of the microbiome in human development. *Gut* **68**, 1108-1114 (2019).

279. W. H. Organization (2019) Breastfeeding and family-friendly policies: advocacy brief. (World Health Organization).
280. E. C. Deehan, J. Walter, The fiber gap and the disappearing gut microbiome: Implications for human nutrition. *Cell* **27**, 239-242 (2016).
281. E. D. Sonnenburg, J. L. Sonnenburg, Starving our microbial self: The deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. *Cell Metab* **20**, 779-786 (2014).
282. J. L. Sonnenburg, E. D. Sonnenburg, Vulnerability of the industrialized microbiota. *Science* **366**, eaaw9255 (2019).
283. P. Markowiak, K. Śliżewska, Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients* **9**, 1021 (2017).
284. M. E. Sanders, D. J. Merenstein, G. Reid, G. R. Gibson, R. A. Rastall, Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. *Nature reviews Gastroenterology & hepatology*, 1-12 (2019).
285. P. Vangay *et al.*, US immigration westernizes the human gut microbiome. *Cell* **175**, 962-972. e910 (2018).
286. M. G. Bublitz *et al.*, Food access for all: Empowering innovative local infrastructure. *Journal of Business Research* **100**, 354-365 (2019).
287. M. S. Wetherill, K. C. White, H. K. Seligman, Nutrition-focused food banking in the United States: a qualitative study of healthy food distribution initiatives. *Journal of the Academy of Nutrition and Dietetics* **119**, 1653-1665 (2019).
288. J. G. Mills *et al.*, Urban habitat restoration provides a human health benefit through microbiome rewilding: the Microbiome Rewilding Hypothesis. *Restoration ecology* **25**, 866-872 (2017).
289. G. A. Rook, Regulation of the immune system by biodiversity from the natural environment: an ecosystem service essential to health. *Proceedings of the National Academy of Sciences* **110**, 18360-18367 (2013).
290. A. Carroll-Scott *et al.*, Disentangling neighborhood contextual associations with child body mass index, diet, and physical activity: the role of built, socioeconomic, and social environments. *Social science & medicine* **95**, 106-114 (2013).
291. G. Mhuireach *et al.*, Urban greenness influences airborne bacterial community composition. *Science of the total environment* **571**, 680-687 (2016).
292. D. M. Patrick *et al.*, Decreasing antibiotic use, the gut microbiota, and asthma incidence in children: evidence from population-based and prospective cohort studies. *The Lancet Respiratory Medicine* (2020).
293. R. J. Patrick, Uneven access to safe drinking water for First Nations in Canada: Connecting health and place through source water protection. *Health & place* **17**, 386-389 (2011).
294. S. P. Luby *et al.*, Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomised controlled trial. *The Lancet Global Health* **6**, e302-e315 (2018).
295. W. F. Owen, R. Carmona, C. Pomeroy, Failing another national stress test on health disparities. *Jama* (2020).
296. A. Benezra, J. DeStefano, J. I. Gordon, Anthropology of microbes. *PNAS* **109**, 6378-6381 (2012).

297. T. Ahmed *et al.*, An evolving perspective about the origins of childhood undernutrition and nutritional interventions that includes the gut microbiome. *Annals of the New York Academy of Sciences* **1332** (2014).
298. R. W. Boyd, E. G. Lindo, L. D. Weeks, M. R. McLemore (2020) On racism: A new standard for publishing on racial health inequities. in *Health Affairs Blog*.

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.

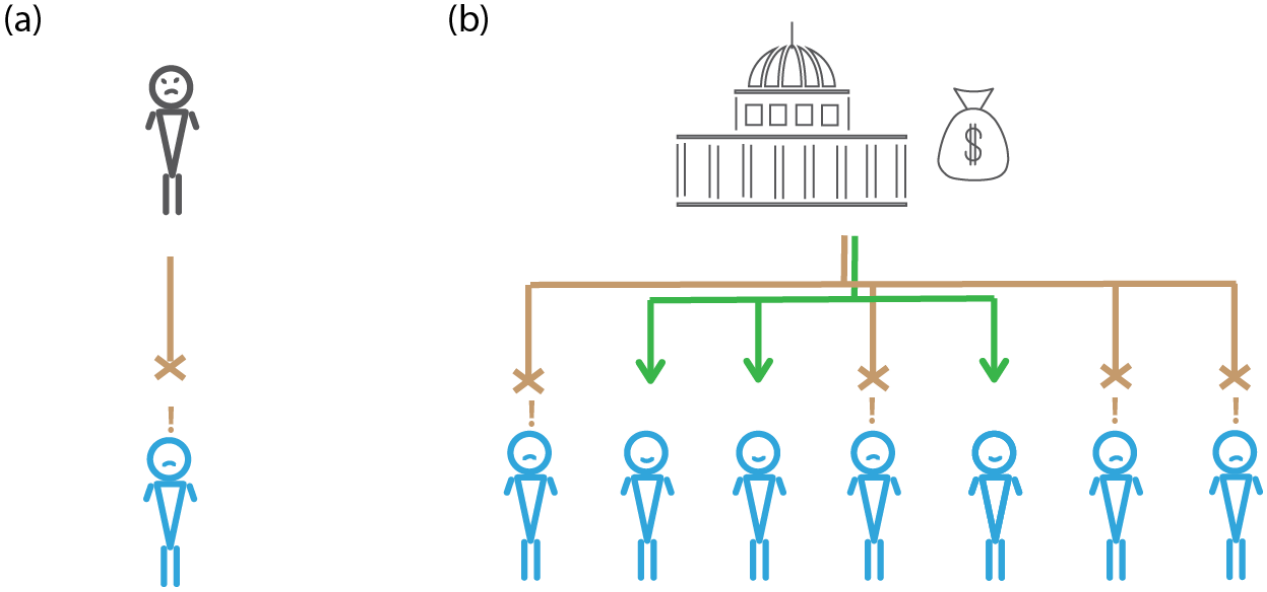

Figure 2. Socially-determined environments are likely to affect health via impacts on the gut microbiome across multiple life stages. Policies aimed at reducing health inequities should therefore consider host-microbe interactions to increase efficacy.

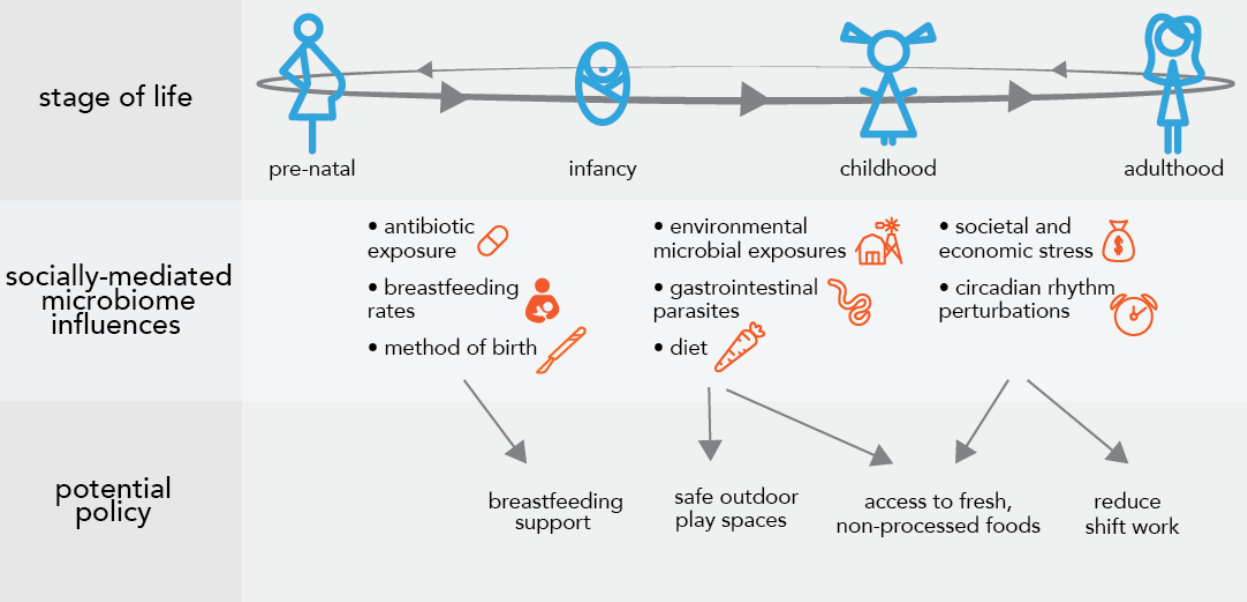

Figure 3. Given that the gut microbiome is associated with many of the chronic diseases in which inequities are observed, it represents a potential target for intervention. Two distinct approaches to using the gut microbiome for reducing health inequities are (a) developing targeted microbiome therapies 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.

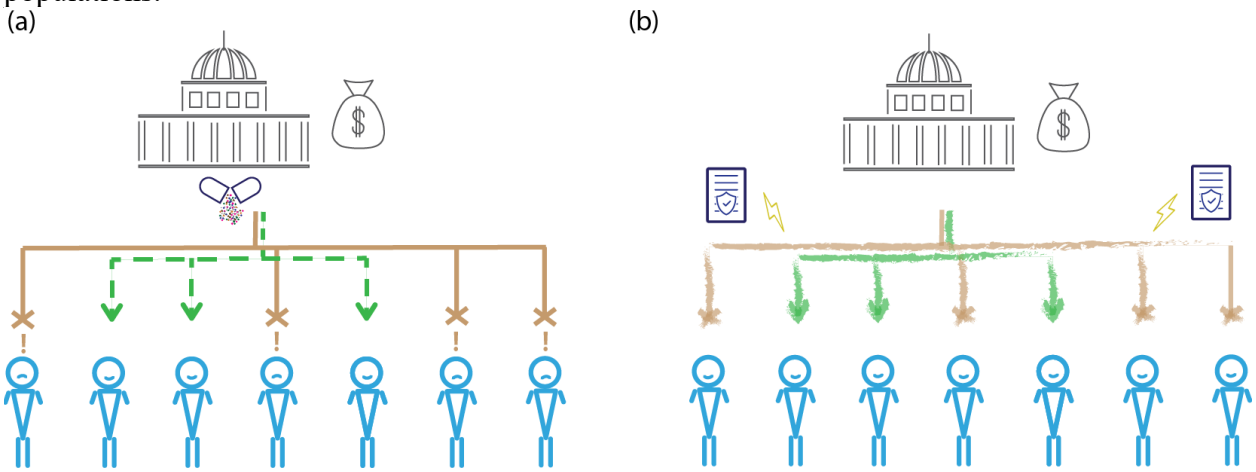

Figure 4. Although more research is necessary, playgrounds made with (a) recycled rubber and plastic are more likely to promote exposure to simple, 'artificial' microbial communities that interact in unknown ways with the gut microbiome and health while those that incorporate (b) features such as grass, 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.