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▶ To cite this version:

Katherine Amato, Marie-Claire Arrieta, Meghan Azad, Michael Bailey, Josiane Broussard, et al.. The human gut microbiome and health inequities. Proceedings of the National Academy of Sciences of the United States of America, 2021, 118 (25), pp.e2017947118. 10.1073/pnas.2017947118. hal-03369892

HAL Id: hal-03369892 https://hal.science/hal-03369892

Submitted on 8 Oct 2021

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The Human Gut Microbiome and Health Inequities 1

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- 53 Abstract: Individuals who are minoritized as a result of race, sexual identity, gender, or
- 54 socioeconomic status experience a higher prevalence of many diseases. Understanding the
- 55 biological processes that cause and maintain these socially-driven health inequities is essential
- 56 for addressing them. The gut microbiome is strongly shaped by host environments and affects
- 57 host metabolic, immune, and neuroendocrine functions. The gut microbiome is thus an important
- 58 pathway by which differences in experiences caused by social, political, and economic forces
- 59 could contribute to health inequities. Nevertheless, few studies have directly integrated the
- 60 human gut microbiome into investigations of health inequities. Here we argue that accounting for
- 61 host-gut microbe interactions will improve our understanding and management of health
- 62 inequities, and that health policy must begin to consider human-microbiome interactions as
- 63 important pathways linking social environments to population health.

64

65 **1. Introduction**

66 Inequities in morbidity and mortality are a persistent challenge among populations in the 67 US and globally. Some of these disparities trace to underlying inequities related to 68 socioeconomic status (SES) (1). For example, in the US, men in the highest and lowest percentile 69 of income have an approximately 15 year difference in life expectancy (2). In addition to SES, 70 self-identified race, sexual identity, and gender status also are powerful predictors of many 71 health outcomes (3-5). For instance, controlling for SES, Black adults have triple the odds of 72 being diagnosed with diabetes compared to white adults (4), and LGBTQ adults are twice as 73 likely to report multiple risks for cardiovascular disease than heterosexual individuals (3). 74 Importantly, although racial health inequities are sometimes assumed to have biological 75 underpinnings, race is a social construct created to control access to power and resources; it has 76 no robust genetic or biological foundation (6-8). Therefore, traditional concepts of heritability or 77 ancestry cannot account for intergenerational patterns in health inequities. Instead, biological 78 patterns observed across minoritized populations are driven by the influences of social forces on 79 physiology and health (9). Personal experiences of racism and discrimination create chronic 80 stress that results in negative health outcomes (10). Similarly, discriminatory laws and policies 81 hinder access to resources like health care, employment, and education, and foster the 82 development of segregated neighborhoods with reduced access to fresh, unprocessed foods, 83 limited space for safe exercise, and increased exposure to noise or chemical pollutants (5, 10-12). 84 Knowledge of the importance of these environmental and social inequities in driving 85 disparities in health outcomes has stimulated investigations into the biological pathways that link 86 lived experiences to altered health. This research is critical for clarifying the causes of unequal 87 burdens of disease across demographic groups and is an important precursor to devising effective

88 strategies to reverse or ameliorate their effects. To date, much work in this area has focused on 89 the impact of chronic stressors, such as discrimination, on bodily systems like stress physiology 90 or inflammation that drive chronic disease risk (10, 13). Structural disparities in experiences that 91 influence nutrient intake, blood pressure regulation, or carcinogenic exposure similarly 92 contribute to health inequities in well-described ways (5, 10-12). This biological embodiment of 93 structural inequity is increasingly recognized as manifesting across multiple time scales: adults 94 exhibit biological symptoms of their current environments, but adverse early life environments 95 also can lead to persistent biological changes that increase adult risk for negative health 96 outcomes including coronary heart disease, stroke, metabolic disease, and osteoporosis (14). 97 Adding to this established literature, the recent rise of work on the gut microbiome 98 (GM)—the community of microbes that inhabits the human gastrointestinal tract—is revealing a 99 novel set of pathways through which environmental exposures could contribute to health 100 inequities. The composition and function of the GM is strongly shaped by host lifestyle and 101 environment (15), including the foods we eat (16), medications we take (17), types of houses we 102 live in (18), and people we spend time with (19). As these factors change with time, so does the 103 GM, making it a plastic component of human biology. As a result, the adverse environmental 104 effects of structural discrimination on the basis of SES, race, or gender/sexual identity are likely 105 to be reflected in the GM of minoritized populations (Fig. 1).

In turn, the GM contributes to myriad aspects of host biology. It confers protection from pathogens through colonization resistance, influences host nutrition and metabolism, trains and modulates immune function, and contributes to patterns of brain development and behavior (20-24). As a result of these diverse effects, alterations to the GM during both infancy and adulthood are recognized as leading to dysregulation of immune, metabolic and neuroendocrine processes

111 involved in a range of health disparities, including obesity, diabetes, atherosclerosis, asthma, 112 allergies, depression and anxiety (25-29). Although causality can be difficult to establish, a 113 growing list of studies now provide evidence that an altered GM is a causal factor in disease (28, 114 29). In addition, because some of the pathological states that result from an altered GM (e.g. 115 obesity, inflammation, diabetes) can have adverse effects on the gestational environment 116 experienced by the next generation and because microbes can be passed from parents to 117 offspring (30, 31), the GM is increasingly recognized as potentially influencing health in an 118 intergenerational fashion. These relationships raise the possibility that differences in the GMs of 119 minoritized populations both reflect patterns of structural inequities and amplify them by 120 negatively impacting health outcomes (Fig. 1).

121 Despite these potentially important links, and calls for attention to them (32, 33), few 122 studies have directly investigated the role of the GM in health inequities. Here, we aim to explore 123 the potential that this work holds, and to encourage the integration of the GM into future studies 124 of health disparities. After briefly summarizing concepts of GM health, we review evidence from 125 past studies linking the GM to health inequities. We then outline the probable effects of 126 environmental disparities on GM composition and function and discuss known contributions of 127 the GM to nutrition and metabolic diseases, asthma, cognitive development, and mental illness. 128 We also consider the potential role of the GM in COVID-19 morbidity and mortality. We 129 conclude by explaining how the plasticity and responsiveness of the GM makes it a particularly 130 useful lever for interventions and examine both the opportunities and challenges for using GM 131 research to inform health policies aimed at reducing the burden of health inequities. 132

132

133 2. GM ecology and health

134 Many specific microbial mechanisms of disease are still not fully understood, and there 135 are no known microbes that are present in all healthy people or absent from all unhealthy people. 136 As a result, identifying 'healthy' and 'unhealthy' GM states is difficult. However, because the GM 137 is an ecological community of thousands of interacting microbial taxa, ecological theory 138 provides valuable guiding principles. Importantly, the most influential GM impacts on host 139 health are likely to be emergent community functions that result from the complex ecological 140 interactions of multiple microbial taxa. As a result, a change in the relative abundance of a single 141 microbial taxon may or may not affect community function depending on the composition of the 142 rest of the community (34). Instead, the relative abundances of multiple interacting microbial 143 taxa, as well as the stability of the overall community across time and its resilience to 144 disturbance, more strongly shape GM function and, ultimately, host health (35). 145 Because basic ecological theory posits that more complex ecological communities are 146 also more stable and resilient, GM diversity is often used as a proxy for health (36). However, as 147 observed in the infant gut, reduced GM diversity does not always have adverse effects on the 148 community or host health (37). Therefore, concepts such as modularity, or interconnectedness, of 149 the GM are also useful for describing GM community structure and associated impacts on hosts 150 (35). Additionally, identifying keystone microbial taxa or functions that promote modularity 151 and/or disproportionately contribute to emergent community function can provide important 152 insight into host health (34).

153

154 **3. Evidence linking GM to health inequities**

To date, the majority of studies of the human GM have had a narrow biomedical focus or describe broad population-level trends in response to environmental variation. Few studies have 157 assessed GM variation across demographics likely to experience structural inequities, and only a 158 handful have attempted to link socially-attributed variation in the GM to host health (38-42). 159 Nevertheless, the existing literature provides growing evidence that the social and environmental 160 gradients known to predict and contribute to health inequities also predict GM community traits 161 (see Table 1). For example, across globally diverse populations, different measures of SES have 162 been associated with distinct GM traits in both adults (42-44) and children (45-49)(but see (50)). 163 Similarly, the GM consistently varies with race (e.g. Asian, Black, Hispanic, white) and/or 164 ethnicity/ancestry (Arapaho, Cheyenne, Dutch, Ghanaian, Moroccan) in adults (38, 39, 41, 51) 165 and children (46, 47, 52, 53).

166 Three studies in particular have provided strong evidence linking structural inequities to 167 GM variation in the context of SES. One of the first studies in this area demonstrated that after 168 adjustment for demographic and lifestyle confounders, neighborhood SES in Chicago explained 169 12-25% of the variation in adult GM composition (43). Specifically, participants in a higher-SES 170 neighborhood had greater GM diversity and altered relative abundances of key bacterial taxa. A 171 larger subsequent study in the UK likewise reported a positive association between neighborhood 172 SES and GM diversity. Importantly, this association was observed in a discordant-twin analysis, 173 which minimizes the possibility of the main effects being confounded by shared genetic or 174 family influences (44). This paper also found that individual SES was positively correlated with 175 GM diversity, and the relative abundances of some bacterial taxa. Finally, a study of 14 districts 176 in China showed that the relative abundances of taxa accounting for 38.8% of the GM varied in 177 response to personal yearly income and spending (42).

Despite the important contributions of these papers, however, most studies of GM
patterns in minoritized populations do not operationalize structural inequities, and small sample

180 size reduces power to disentangle common co-variates. Further, while race and ethnicity/ancestry 181 are often used interchangeably, they are distinct concepts that interact differently with biology. 182 While some ethnic groups are minoritized, their shared ancestry may lead to genetic differences 183 that contribute to patterns in health inequities in addition to the social experiences of racism and 184 discrimination. In contrast, biological patterns across racial groups primarily reflect the impact of 185 racism and discrimination. As a result of these weaknesses and inconsistencies, the relative 186 importance of personal experiences of racism and discrimination versus structural impacts on 187 environments for the GM remains largely unknown. Similarly, the scale (i.e. household, 188 neighborhood, and beyond) at which structural inequities might affect the GM is unclear. 189 Nonetheless, the existing literature demonstrates that the same social gradients that predict 190 disparities in major classes of disease also predict variation in the GM. These relationships 191 underscore the likely role of the GM in mediating socially-driven health disparities.

192

193 4. Potential pathways to disparities in the GM

194 Population differences in GM communities are established in response to a combination 195 of factors that include intergenerational transmission during infancy as well as ongoing effects of 196 environment and lifestyle factors from infancy into adulthood. As a result, structurally imposed 197 differences in lifestyle and environmental factors can preclude the establishment of appropriate 198 GM communities as early as birth. Infants are typically first exposed to microbes during labor 199 and birth via contact with the maternal vaginal and fecal microbiome (37, 54, 55). Cesarean 200 births are more frequent in low-SES and minoritized populations (56), and babies born via 201 cesarean section exhibit altered GM developmental trajectories during the first year of life as a

202 result of lower maternal microbial input compared to vaginal delivery, along with increased203 exposure to antibiotics (57).

204 Practices such as skin-to-skin contact and breastfeeding offer further opportunities for 205 microbial exchange that may promote the establishment of keystone GM taxa and functions (57, 206 58). Breast milk is a source of probiotic bacteria, as well as of prebiotic oligosaccharides that 207 help foster the establishment and growth of beneficial microbes in the infant gastrointestinal tract 208 (59). Mothers in low-SES or minoritized populations may engage in less skin-to-skin contact and 209 shift from breastmilk to formula earlier as a result of maternal work pressure or lack of relevant 210 health information (60, 61). At three months, breastfed babies have a distinct GM compared to 211 formula fed babies, including lower microbial diversity and increased relative abundances of 212 beneficial microbes (62, 63). The combined loss of protective microbial factors in breastmilk and 213 increased exposure to waterborne pathogens and toxins [e.g., the Flint, Michigan water 214 contamination crisis (64)] may place children at higher risk for negative alterations in the GM. 215 As infants mature, GM composition stabilizes, and by approximately three years of age, 216 the GM resembles that of an adult (62). Both before and after this age, a number of factors are 217 known to influence the GM. Close physical proximity to other people and/or household animals 218 leads to increased GM similarity in both adults and infants (19, 65). Hygiene, sanitation, and 219 medical practices can impact the GM, often by disrupting community composition and reducing 220 diversity (66, 67). Finally, although environmental factors appear to play the strongest role in 221 shaping the human GM (15), host genotype has been associated with variation in a subset of the 222 GM (68, 69).

Diet has one of the largest known impacts on the GM, altering GM composition on timescales from hours to years (16, 70). Specifically, high-fat, low-fiber diets that tend to be

225 more geographically and economically accessible to low-SES and minoritized families (71) have 226 been shown to reduce GM diversity and negatively alter GM function (16, 70, 72). Increased 227 time spent indoors and reduced exposure to outdoor environmental microbes is also believed to 228 reduce GM diversity (73, 74), and low-SES and minoritized populations generally have less 229 access to safe, outdoor green space compared to higher SES groups (75). Various forms of sleep 230 disruption alter the GM (76, 77), which puts individuals with unusual sleep-wake cycles like 231 shift workers, who are often disproportionately from minoritized populations (78), at risk for 232 altered GM composition and associated diseases. Finally, low-SES and minoritized populations 233 experience high levels of chronic stress (10, 11), which can result in altered GM composition, 234 such as reduced relative abundance of lactobacilli (79-83).

235

236 5. Pathways through which the GM can contribute to health outcomes

Determining the GM's contribution to health inequities in human populations, and harnessing this information to inform policy, will require strong evidence that variations in the GM exert a causal impact on specific health outcomes. Here, we explore the potential role of the GM in shaping health conditions with known disparities, including undernutrition, metabolic diseases, asthma, neurodevelopmental and mood disorders, and COVID-19.

242

243 Child Undernutrition

244 Child undernutrition affects more than 50 million individuals under five years of age, 245 contributes to nearly half of all global child deaths (84), and is most common in low-SES and 246 minoritized populations (85). Severe cases are surprisingly refractory to recommended 247 nutritional-based therapies, with long-term sequelae that include stunting, decreased earning

potential, impaired vaccine responses, and increased long-term risks of obesity, metabolic
syndrome, and cognitive deficits (86).

250 Undernutrition is believed to have multiple biological causes, including both macro- and 251 micronutrient deficiencies. In low resource settings, infection by enteropathogens that decrease 252 nutrient absorption and assimilation while simultaneously increasing immune energy needs is a 253 primary cause of undernutrition (87). As a result, inequities in undernutrition are commonly 254 associated with structural variation in sanitation and availability of safe, treated water as well as 255 maternal, prenatal, and perinatal factors affecting the function of the immune and endocrine 256 systems (88). However, other mechanisms may also be at work. For example, the GM influences 257 the establishment of enteropathogens by reducing their success via competitive exclusion or 258 pathogen-defense functions (24). Therefore, variation in early life GM development as a result of 259 the factors outlined above could dictate susceptibility to infection and its sequelae. The 260 inflammation resulting from infection can further alter the GM, increasing risk of future infection 261 and further impairing other aspects of physiology (89). Even in the absence of active infection at 262 the time of sampling, undernourished children have GMs with reduced diversity and altered 263 composition (90-92). These GMs can causally impair growth when introduced into germ-free 264 mice (90, 91). Importantly, growth impairment can be ameliorated in both mice and piglets 265 through the use of prebiotic foods (93) and probiotic administration of Lactobacillus plantarum 266 (94).

267

268 Diseases related to overnutrition

269 More than half of the world's adult population is overweight or obese, and the related 270 conditions of diabetes and cardiovascular disease are now the leading causes of death globally

(95). The rise of these conditions has been particularly rapid in minoritized populations (96), and
it is unclear why individuals and populations vary in susceptibility when faced with similar diets
and environments (95). Factors such as stress and sleep disruption, cesarean births, and early life
antibiotics have been implicated (97-100).

275 The GM is one potentially important pathway for understanding these relationships. In 276 general, studies associate an altered, low diversity GM with increased risk for obesity and 277 diabetes (28, 101), and the GMs of obese human individuals can causally induce obesity in mice 278 (28). These effects may operate via multiple mechanisms, including excess host-accessible 279 energy production by microbes in the form of short-chain fatty acids (SCFAs), alteration of host 280 metabolic programming via production of SCFAs and other metabolites, and promotion of host 281 inflammation (28, 102, 103). Disparities in environmental factors that result in these GM traits 282 could therefore contribute to disparities in metabolic disease. While many of the environmental 283 factors described earlier could play important roles in affecting the GM in this context, high-fat, 284 low-fiber diets that can be prevalent in minoritized populations in settings like the US (71) 285 consistently result in GM signatures that resemble those typical of obesity and metabolic disease 286 (72).

287 Asthma

Asthma affects approximately 14% of children worldwide with incidence increasing by 50% every decade (104). Asthma disproportionately impacts low-SES, minoritized, and urban populations in middle- and high-income countries (105), with more than 80% of deaths occurring in these populations. In addition to its role in mortality, the impact of asthma includes wideranging factors like days lost from school and interference with physical exercise (106). Although genetic susceptibility contributes to asthma pathogenesis in some populations, it only

294 explains a minority of cases (107). Instead, asthma prevalence and severity are linked to a range 295 of environmental factors including reduced exposure to outdoor environments, animals, and 296 helminthic infections, increased incidence of viral and bacterial infections, increased antibiotic 297 exposure, cesarean birth, and formula feeding (107-111). 298 There is accumulating evidence for a role of the GM as mediator between these 299 environmental factors and asthma morbidity. Microbial alterations have been observed in the 300 airways of individuals with asthma (112, 113), and infant GM signatures can be used to predict 301 asthma risk later in life (29, 114, 115). For example, Faecalibacterium, Lachnospira, Veillonella, 302 and *Rothia* are negatively associated with future asthma development in 3-month-old infants 303 (29), and supplementation of these bacteria to germ-free mice colonized with asthma-associated 304 stool samples ameliorates airway inflammation (29). While additional research is needed, 305 research to date has linked asthma morbidity in children to GM-mediated impacts on immune 306 function development and inflammatory responses (109, 116). 307 308 Preterm birth and neurodevelopmental trajectories 309 Despite technology-enabled increases in the survival of extremely preterm (<28 weeks)

infants in the U.S., cognitive outcomes in these individuals are often severely impaired (117,
118). Preterm babies born into low-SES families and/or minoritized populations often have
poorer cognitive outcomes (119). While a number of factors, including access to early life
education (120), likely contribute to these patterns, variation in inflammatory markers in infant
serum is a key area of interest (121, 122).

The GM could play a key role in mediating the relationship between preterm neurodevelopmental outcomes and inflammation. Research in mice has demonstrated that the GM

317 links key immune and neurological pathways in infancy (22), and the composition of the human 318 GM has been associated with neurodevelopmental status at one year of age (123). Additionally, 319 gnotobiotic mice colonized with the GM from human preterm infants experience systemic 320 inflammation, as well as alterations in myelination, neuronal number, and neurotransmission 321 pathways (124). No research to our knowledge has directly linked specific environmental 322 disparities to pre-term neurodevelopmental outcomes. However, if disparities in the 323 environmental factors outlined above affect either the maternal or infant GM, it could alter infant 324 inflammatory profiles, which in turn have well-established effects on cognitive development 325 (125). Additionally, the parental ability to engage with infants in the neonatal intensive care unit 326 via skin-to-skin contact and/or breastfeeding, as a result of professional or personal demands, or 327 infant health status, may also result in disparities in infant microbial exposures.

328

329 Mental health

Mental illness is recognized as one of the largest causes of morbidity globally (126). Depression is the leading cause of disability worldwide, and approximately half of those diagnosed with depression also suffer from anxiety simultaneously (127). Individuals belonging to minoritized populations as well as individuals with reduced economic resources are disproportionately impacted by these conditions (1, 128), and experiential and behavioral factors such as stress and diet are considered among the strongest influences on conditions like depression and anxiety (129, 130).

The GM is emerging as a potentially important mediating pathway for mental illness. In both humans and rodents, individuals with symptoms of depression have distinct GM compositions compared with individuals without symptoms (131, 132), and a depressive

340 phenotype can be induced in rats using a fecal transfer from depressed patients (133). 341 Conversely, probiotics and prebiotics have been shown to ameliorate depressive symptoms in 342 both animal models and humans (134, 135). These relationships are likely associated with the 343 ability of the GM to influence the metabolism of host neurotransmitters and hormones including 344 serotonin, dopamine, GABA, ACTH, and glucocorticoids (136, 137). There is also evidence 345 from mice that gut microbes can directly influence nervous system functioning through 346 interactions with sensory neurons, including the vagus nerve that connects the gut to the brain 347 (138, 139). As a result, the roles of diet and stress in mental health are likely mediated, at least in 348 part, through the GM (140), and disparities in mental illness likely reflect disparities in diet and 349 stress that impact the GM.

350

351 The role of the GM in infectious disease and the COVID-19 pandemic

352 The COVID-19 global pandemic caused by coronavirus SARS-CoV-2 represents one of 353 the most recent and acute examples of health inequities. Although all populations are susceptible 354 to the disease, Black and Latino populations in the U.S. are exhibiting higher infection and 355 mortality rates compared to their white and Asian counterparts (141-143). These disparities are 356 likely due to a combination of factors including limited opportunities to engage in isolating 357 behaviors to reduce exposure, increased probability of underlying comorbidities perpetuated by 358 structural inequities such as obesity, cardiovascular disease, and diabetes, and reduced access to 359 healthcare (141-143).

Although there is still much to learn about this virus and its interactions with hosts, it is likely that the GM influences COVID-19 susceptibility and outcomes (144). To begin with, many of the underlying comorbidities that increase risk of morbidity and mortality from COVID-

363 19 appear to be shaped by host-microbe interactions, as described previously. Additionally, since 364 data from mice demonstrate that the GM trains the immune system and affects host responses to 365 other respiratory viruses such as the influenza virus (145, 146), it is similarly likely to play a 366 role, either directly or indirectly via effects on other disease sequelae, in moderating host 367 immune responses to SARS-CoV-2. For example, COVID-19 mortality rates appear to be 368 strongly influenced by host susceptibility to out-of-control inflammatory responses, and the GM 369 can directly influence these responses (147, 148). Similarly, COVID-19 can infect the gut as well 370 as the respiratory tract (149), allowing for direct interactions between the GM and virus-infected 371 cells..

372

373 6. Importance of early life and intergenerational GM dynamics on health

374 The studies reviewed above show that a range of environmental and lifestyle factors at various 375 points in the lifecycle can influence the GM in ways that influence risk for multiple disease end 376 points. Although this work confirms that the GM exhibits responsiveness and plasticity to 377 changing environments throughout life, GM community establishment during infancy is likely to 378 be particularly important given emerging evidence that it is not only which microbial taxa and 379 genes that are established, but when in the lifecycle, that matters to the long-term disposition of 380 immune, metabolic, and neurological states (20, 150, 151). For example, mice that are not 381 exposed to key microbial strains during early life do not develop appropriate immune and 382 nervous system function, even if they are exposed to those microbes later (151, 152). Likewise, 383 mice exposed to low-dose antibiotics during early life exhibit altered metabolism and immune 384 function even after their GM returns to its original state (153). Intergenerational GM dynamics 385 also appear to be important. Mice fed a low fiber diet lose fiber-dependent GM taxa cumulatively

across generations (154). Some studies in mice also suggest that mothers may pass on
inflammatory bowel disease, metabolic disease risk, or stress phenotypes to their infants via the
GM (97, 155, 156). Therefore, to the extent that findings in mice apply to humans, the
determinants of GM composition and its impact on health may not be limited to a single
generation.

391

392 7. Leveraging the GM to address health inequities

393 The growing evidence that the GM is a link between social environments and diseases 394 characterized by marked disparities points to new levers that could be harnessed to help 395 ameliorate their effects. However, key gaps remain that must be addressed before the GM can be 396 effectively used to guide interventions. For example, current studies describe either the 397 relationship between the social dynamics of SES/race/gender identity and the GM, or the 398 relationship between the GM and health. No study simultaneously and empirically assesses 399 SES/race/gender identity, the GM, and health outcomes to determine what facets of health 400 inequities are actually mediated by the GM and the relative importance of the GM versus other 401 potential mediating pathways. Similarly, inequality manifests at multiple levels of organization, 402 exposing people to neighborhood, household, workplace, and individual factors that can alter the 403 GM. However, no GM study has quantitatively examined the relative importance of exposures at 404 these different levels or the extent to which they interact with each other. Not only does this gap 405 limit scientific understanding of personal versus structural drivers of health inequities, but it 406 inhibits the development of effective interventions.

407 To begin to fill these gaps, future studies should engage a multidisciplinary approach that 408 melds GM research with fields like epidemiology and the social sciences (32) to strengthen study

409 design and quantitative assessment of inequities. For example, SES is measured differently 410 across many of the existing studies and often targets a narrow range of factors such as income 411 and education (Table 1). Similarly, in studies of race and gender/sexual identity, the role of 412 experiences with racism and discrimination—either through personal encounters or structural 413 inequities—has not yet been addressed directly. The social sciences can provide critical guidance 414 in these areas. Additionally, the declining costs of GM sequencing will facilitate larger sample 415 sizes and higher resolution microbial data to leverage epidemiological approaches to tease apart 416 the independent effects of multiple environmental determinants. Quasi-experimental approaches 417 (e.g. discordant twin or adoption studies), interventions (e.g. randomized cash-transfer and 418 housing-voucher experiments), and controlled animal model experiments (e.g. social dominance 419 challenges) currently used to study health inequities outside the microbiome context can also be 420 used to further strengthen causal inference.

421 As evidence linking the GM to the embodiment of structural inequities in minoritized 422 populations amasses, it will open up new opportunities for intervention to ameliorate or reverse 423 health inequities. Although much basic research remains to be done, we imagine that future 424 interventions will take multiple forms that could work in complementary ways to reduce the 425 disproportionate societal burden of many common diseases. Specifically, we believe that the 426 development of interventions should include a combination of research-based therapies and 427 policy updates that use a biomedical approach to target known keystone GM traits that 428 disproportionately contribute to host health as well as an ecological approach to support the 429 development and maintenance of stable, resilient GM communities (Fig. 2).

430

431 Targeted biomedical interventions

432 Targeted GM interventions for specific diseases are receiving growing attention. For 433 example, Lactobacillus and Bifidobacterium probiotics are being used in multiple clinical trials 434 as a treatment for depression with mixed outcomes (157), and fecal transplants are a highly 435 effective therapy for *C. difficile* infection (158). Nevertheless, substantial research is necessary 436 before these approaches can be routinely implemented. Even in the relatively simple case of 437 probiotics, the microbial taxa of interest are only established in the gut in a subset of people, and 438 it remains unclear whether there are durable health benefits (159, 160). Efforts may need to focus 439 on keystone GM taxa that have large positive effects on their host, such as Bifidobacterium 440 *longum* subsp. *infantis* in breastmilk (161). Alternatively, researchers should look past microbial 441 taxonomy to identify specific microbial genes, proteins or metabolites that are associated with 442 particular beneficial or detrimental effects (162).

443 While these personalized treatments and interventions have the potential to transform our 444 ability to treat many of the diseases in which disparities are observed, the current practices 445 surrounding their development and distribution limit their power to substantially alter patterns of 446 health inequity. First, most GM biomedical research targets relatively homogenous populations 447 that consist largely of affluent adults of European descent and does not consistently account for 448 the rich cultural and environmental contexts in which people and their GMs exist. Given the 449 extent to which structural forces, acting through ecological, behavioral, and experiential factors, 450 shape the GM, this narrow approach will result in emerging therapies that will have untested 451 utility in populations experiencing the highest burdens of GM-mediated disease. Challenges with 452 generalizability in the GM field more broadly underscore this risk. For instance, research from 453 China has demonstrated that predictive models of health designed using the GM of one 454 population with specific cultural and environmental traits cannot easily be translated to another

455 (163). Therefore, GM research must incorporate knowledge from the health inequities field and 456 begin to account for cross-population differences in the context of both basic research and 457 applied clinical trials. Federal policies that prioritize funding for the development of targeted GM 458 therapies for populations experiencing disproportionate burdens of disease would advance these 459 efforts.

Additionally, targeted GM therapies are likely to be distributed through channels constrained by unequal access, such as health care or prescription medications, which are already recognized as important drivers of population health disparities. As a result, populations with the greatest potential to benefit from these interventions may be less likely to have access to them. Here, transformative policy interventions that strive for universal access to emerging health technologies, and to healthcare more generally, will be essential for ensuring that new GM developments reach the populations that would most benefit from them.

467

468 Ecologically-inspired interventions

469 To complement targeted GM therapies, ecologically-inspired interventions that support 470 the development and maintenance of a stable, resilient GM community may be important tools 471 for leveraging the GM to address health inequities. Specifically, policy interventions should be 472 designed to counteract structurally-induced disparities in environments and behaviors that affect 473 the development of robust GM communities in minoritized populations. While some policies, 474 such as antibiotic stewardship programs and improvements to water and sewage infrastructure, 475 already are informed by knowledge of microbial impacts on health (164, 165), most health 476 policies do not integrate goals motivated by an understanding of host-environment-GM 477 interactions. Explicitly integrating the GM into both new and existing policy at local, state and

federal levels is likely to fill critical gaps and substantially improve associated health outcomes.
Continued research is necessary to optimize these approaches by identifying keystone GM traits
and determining the most effective pathways for promoting stable and resilient GM ecologies
(166). Nevertheless, our current knowledge of the factors promoting diverse, interconnected GM
ecologies, particularly during early life, provide an important foundation upon which new policy
perspectives can be built as the field advances (Fig. 1).

484 Breastfeeding is an excellent example of an area in which our current understanding of 485 the GM can be used to improve health policy. In many global settings, breastfeeding rates tend to 486 be lower among low-SES or minoritized populations (60, 61). Programs to support breastfeeding 487 for mothers have the potential to reduce health inequities through multiple mechanisms (167), 488 including by facilitating the development of stable and resilient GM communities in infants. In 489 the US, many workplace efforts to facilitate breastfeeding provide space and resources for 490 mothers to express milk. While this practice partially facilitates infant GM development through 491 the provision of breastmilk, it also reduces physical contact between mothers and infants, which 492 may alter microbial transmission patterns. It is similarly unclear whether freezing, thawing, and 493 reheating breastmilk affects microbes and other bioactive human milk components essential for 494 the normal development of the infant GM (58). Recent movements in the U.S. to guarantee a 495 minimum period of paid maternal leave, reflecting policies implemented in nearly all other high 496 income countries, could substantially diminish risks for developing a range of conditions that 497 have been linked to reduced breastfeeding and altered GM ecology, including obesity, diabetes 498 and asthma (167).

499 Similarly, policies aimed at reducing health disparities by improving access to affordable,
500 non-processed foods could be tailored to maximize beneficial impacts on the GM. Existing

501 nutritional policies tend to emphasize the nutritive importance of lean protein sources and fresh 502 produce and do not recognize the role of food in shaping GM ecology. However, as one 503 example, high-fiber diets are strongly associated with diverse, interconnected GM communities 504 (70, 168, 169). This information should be used to update policy and improve access to high-505 fiber, 'microbe-friendly' foods through food banks and food supplement programs such as WIC 506 in the U.S. The feasibility of such efforts would be enhanced by the design of fresh food 507 production and delivery systems that are more efficient, flexible, and resilient to disruption than 508 those currently in use (170, 171).

509

510 6. Conclusion

511 Although there are many biological systems through which socially-determined 512 differences in environments lead to health inequities, the GM represents an important set of 513 pathways that have yet to be fully explored. Given its sensitivity to myriad environmental factors 514 as well as its prominent role in shaping host physiology and health, the GM is likely to both 515 respond to and perpetuate the structural inequities created by racism and other forms of 516 discrimination. Because the environments that drive GM composition are modifiable, the GM 517 represents an important new tool for mitigating the impact of structural inequities and their 518 downstream health consequences. In this context, both biomedical approaches targeting 519 individual GM taxa and functions, as well as ecological approaches promoting the maintenance 520 of stable and resilient GM communities, should be combined with policy interventions aimed at 521 equalizing access to resources, environmental exposures, and disease risk and adopting an anti-522 racist stance in healthcare. Achieving this goal will require collaborations between GM 523 researchers and those in fields specializing in the assessment of social environments and their

impacts on health, including epidemiology and health-focused fields in the social sciences (172,
173), as well as medical doctors, nurses, and policy makers that can put key findings into
practice.

527

6. Acknowledgements CK and KRA thank the HCEO global working group for supporting a

529 workshop that catalyzed this collaboration. Other acknowledgements are in supplemental

530 material.

- 532 Figure 1. Experiences of discrimination across multiple scales are likely to affect the structure
- and function of the microbiome through a variety of pathways across multiple life stages. Given
- 534 links between the microbiome and metabolism, immunity, and nervous system function,
- 535 microbiome perturbations incited by discrimination can result in negative health outcomes.
- 536 These include acute symptoms, various chronic diseases, and heterogenous immunity to
- 537 pathogens including respiratory viruses. Behaviors and treatments associated with these factors
- 538 can feed back to further alter the microbiome, creating a positive feedback cycle. (Created with
- 539 BioRender.com)
- 540



542 Figure 2. The gut microbiome represents a potential target for interrupting health inequities via 543 complementary approaches that integrate both research and policy. These approaches include 544 targeted biomedical interventions that aim to introduce key microbial taxa or functions into an 545 altered microbiome and ecologically-inspired interventions that support the environmental 546 conditions favoring the development of a stable and resilient microbiome community. A variety 547 of stakeholders and key considerations for addressing structural inequities operate within both 548 the policy and research toolkits that contribute to these interventions. Although often considered 549 separately, they are interrelated. We list some key examples here. (Created with BioRender.com) 550



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