Received: 11 February 2021 | Revised: 12 March 2021 | Accepted: 16 March 2021

DOI: 10.1002/bies.202100049

BioEssays

PROBLEMS AND PARADIGMS

Prospects & Overviews

Global climate change, diet, and the complex relationship between human host and microbiome: Towards an integrated picture

Francesco Catania[1] | Jan Baedke[2] | Alejandro Fábregas-Tejeda[2] | Abigail Nieves Delgado[3,4] | Valerio Vitali[1] | Le Anh Nguyen Long[5]

[1] Institute for Evolution and Biodiversity, University of Münster, Münster, Germany

[2] Department of Philosophy I, Ruhr University Bochum, Bochum, Germany

[3] Knowledge, Technology & Innovation, Wageningen University, Wageningen, The Netherlands

[4] Freudenthal Institute, Utrecht University, Utrecht, The Netherlands

[5] Department of Public Administration, University of Twente, Enschede, The Netherlands

Correspondence
Francesco Catania, Institute for Evolution and Biodiversity, University of Münster, Hüfferstrasse 1, 48149 Münster, Germany.
Email: francesco.catania@uni-muenster.de
Jan Baedke, Department of Philosophy I, Ruhr University Bochum, Universitätsstrasse 150, 44801 Bochum, Germany.
Email: Jan.Baedke@ruhr-uni-bochum.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Numbers: 281125614/GRK 2220, BA 5808/2-1; ERC Starting Grant Local Knowledge, Grant/Award Number: 851004

Abstract

Dietary changes can alter the human microbiome with potential detrimental consequences for health. Given that environment, health, and evolution are interconnected, we ask: Could diet-driven microbiome perturbations have consequences that extend beyond their immediate impact on human health? We address this question in the context of the urgent health challenges posed by global climate change. Drawing on recent studies, we propose that not only can diet-driven microbiome changes lead to dysbiosis, they can also shape life-history traits and fuel human evolution. We posit that dietary shifts prompt mismatched microbiome-host genetics configurations that modulate human longevity and reproductive success. These mismatches can also induce a heritable intra-holobiont stress response, which encourages the holobiont to re-establish equilibrium within the changed nutritional environment. Thus, while mismatches between climate change-related genetic and epigenetic configurations within the holobiont increase the risk and severity of diseases, they may also affect life-history traits and facilitate adaptive responses. These propositions form a framework that can help systematize and address climate-related dietary challenges for policy and health interventions.

KEYWORDS
biological adaptation, climate change, diet, evolution, health, holobiont, microbiome, trade-offs

INTRODUCTION

Climate change can impact human health through manifold pathways.[1] Until now, public attention and scientific studies on the implications of climate change for human health center largely on CO_2 emissions and health risks generated by rapid onset climate disasters (e.g., floods, heat waves, and epidemics). While still relatively rare, these disasters are projected to become more frequent and intense as the climate changes.[2–4] Exposure to dangerous conditions during these events is high and survivors may suffer from long-term health crises (e.g., the loss of motor function). However, the various impacts of climate change on human health may also be less perceptible. Its effects may insidiously accumulate over time much like slow onset climate disasters.[5] A failure to account for how climate change may impact human health through quotidian pathways constitutes a significant blind spot in our understanding of the toll that anthropogenic warming can take on humans. One such pathway is diet.

Climate change and developmental pressures influence a number of factors that shape human diet, including crop yield,[6–9] farming practices,[10] and dietary habits.[11,12] Farmers may already be chang-

ing their practices to accommodate to a changing climate, with clear implications for diet. For example, a case study of eight Aymara communities in Bolivia found that farmers were planting less of what they considered more climate vulnerable crop like isaño (*Tropaeolum tuberosum*) while introducing what they perceived to be sturdier crop.[10] What are the consequences of the resulting dietary changes for human health and evolution? While the link between climate change and diet may be well established in the literature, the mechanisms by which dietary changes translate into health consequences and help generate novel phenotypic traits still require elucidation.

Here, we attempt to fill this gap. Dietary intake may influence health through its effects on the host's epigenetics[13–15] (Box 1) and the host's microbiome (see below). Moreover, there are complex epigenetic relationships between host and microbiome, and it is a formal possibility that epigenetic phenomena can impact evolution.[16] On this basis, we put forward a model that accounts for interactions between epigenetic mechanisms and the human microbiome as well as their crosstalk with host genetics. We maintain that conceptualizing humans as flexible ecosystems or holobionts (as commonly done for, e.g., corals[17]) may help reveal some of the consequences that diet-related changes have for human health, and also offers predictions of future generations of human life-history traits and adaptation capacity. In our model, climate change-induced dietary shifts can increase health risks through dysbiosis. At the same time, these processes prompt microbiome reconfigurations that trigger cross-generational adaptive responses to environmental change. As a key pathway to these short- and long-term effects, we identify the microbiome-epigenome-immunity axis. More generally, we propose a mechanistic framework which connects two so-far insufficiently connected debates: the effects of global climate change on diet, and the complex relationship between microbiome, epigenome, and host.

Box 1. Diet, human health, and epigenetics

Diet has a major impact on human health. Variable diets and dietary patterns can modulate inter-individual variability (e.g., increase the risk of cardiovascular diseases).[18] Diet contributes to birth weight,[19] which is a major predictor of infant and child health, and adult disease susceptibility. Diet also affects longevity and reproduction.[20] For example, dietary restrictions—reduction of food intake without starvation—can up-regulate pathways involved in stress response and innate immunity, and down-regulate pathways involved in growth and reproduction across different species.[21–26] Diet can also have long-term, intergenerational consequences.[19,27] Offspring of parents with a compromised immune state due to malnutrition (i.e., over- or under-nutrition) themselves also often suffer immune system perturbations.[28] Further, in response to increased parental dietary energy, offspring display elevated pro-inflammatory and reduced anti-inflammatory and immune regulatory traits.[29] Yet, under certain conditions, dietary changes may also yield opposing, positive effects on the health of future generations. In one example, the grandchildren of a cohort of Northern Swedes who experienced periods of crop failures over multiple generations display lower risk of mortality, cardiovascular diseases, and diabetes compared to the previous generations.[30] Some of these studies hint at epigenetic mechanisms underlying diet-related effects on human health.[14]

FROM DIET TO PHENOTYPE THROUGH THE MICROBIOME

In recent years, the microbiome has emerged as a new mediator between environmental cues (e.g., nutritional patterns) and human health. The human microbiome includes all those bacteria, archaea, fungi, protists, and viruses that colonize, among others, human skin, placenta, uterus, seminal fluid, lungs, saliva, oral mucosa, conjunctiva, and especially the gastrointestinal tract. If we view the human as an integrated ecosystem with its microbiome[31]—a holobiont[32–36]—then, the microbiome renders a vast array of ecosystem services.[37] By ecosystem services we mean that the human microbiome stimulates the immune system and shapes its development,[38–40] contributes to the development and functioning of the nervous system,[41–43] the synthesis of micronutrients,[44] nutrient digestion and absorption, and to energy regulation.[45–50]

The reliability of these ecosystem services hinges on an effective crosstalk between the host and its microbiome, which is influenced by dietary patterns.[51–57] It follows that climate change-induced modifications in diet or life-style may also impact the host's health status, in line with recent suggestions.[58] Indeed, changes in the human gut microbiome (e.g., due to the increasing use of antibiotics in food production) have been associated with the genesis and progression of different disorders[59–61] such as autoimmune diseases,[62–65] cancer,[66] metabolic disorders (e.g.,[60,67]) and mental disorders, like depression,[68] via the so-called "gut-brain axis." The molecular basis of this relationship as well as the range and strength of the linkages between a phenotype and a microbiome's composition and abundance remains, however, unclear.[69]

THE MICROBIOME WITHIN AND ACROSS GENERATIONS

Diverse evolutionary and ecological models of microbiome establishment, stability, and transmission across generations have been proposed.[70–75] The extensive crosstalk between the human host and its resident microbiome suggests that they have co-evolved or may have co-adapted, that is, the human microbiome has co-evolved with the host, adapting to the human ecosystem and developing mutual benefits.[33,34,76,77] Consistent with this view, only a minute subset

of known bacteria phyla occur in the human ecosystem.[78–84] It is also possible that intra-holobiont associations reflect a one-sided process of adaptation (e.g., the host has adapted to its microbes, but the microbes have not adapted to their host).[85,86] But how can co-evolution—let alone one-sided adaptation or co-adaptation—between the microbiome and the human host be achieved? This question is critical for understanding the effects of diet on human health and evolution. Co-evolution implies that the microbiome must be inherited and/or faithfully acquired across generations. But how?

Microbiota configuration is largely shaped in early life.[87,88] In adults, microbiota retain a level of flexibility that may to some degree be modulated by environmental conditions and factors such as the host's genetic background, behavior and life-style, sex, and age.[51,89–93] Thus, the cross-generational recurrence of microbiome components relies, partly at least, on biological processes that unfold in early life. In humans, the maternal environment appears to contribute to the bacterial colonization of the infant gut.[56,94,95] However, this maternal contribution is most likely partial and thus insufficient to guarantee a faithful transmission analogous to genetic information. Stable (environmentally inherited) cultural and behavioral patterns can compensate for inadequate trans-generational stability of host-microbiota relations. For example, stable cultural patterns in feeding practices, delivery modes, and hygiene lead to similar microbial successive colonization during infancy.[96] As it is in other animals, social interactions and networks may open channels for microbial transmission.[97–99] Finally, host genetics may also play an important role in the acquisition, maintenance, and stability of the microbiome, particularly in the gut.[90,100–102] Genetically determined immune traits may, alongside competition between microbial cells, help regulate and maintain appropriate compositions and levels of microbial populations in a given niche space. In sum, vertical and horizontal transmissions alongside host genetics contribute to the microbiome's cross-generational stability.

This list is incomplete. We propose that the host's epigenome constitutes another, so far underexplored, pathway for stabilizing the environment-dependent host-microbiome interaction across generations. The proposed contribution by the host epigenome to microbial colonization is consistent with studies that tie epigenetic changes (e.g., DNA methylation, histone modifications, regulation by noncoding RNAs[103]) to microbiome colonization and functionality.[104] It also aligns with reports in which microbiome-altering epigenetic modifications are associated with the genesis of diseases.[105,106] Additionally, the host epigenome may both shape and be shaped by the acquired microbiota. The acquired microbiota can influence host appetite, feeding behavior, and food choice (e.g.,[107,108]), which in turn affect gene regulation and regulate the immune response.[109]

Thus, we suggest that not only may the microbiome be faithfully transmitted and acquired across generations through various modes and channels; it can also remodel the host epigenome. This epigenetic remodeling influences offspring development, effectively linking current environmental changes such as dietary shifts to future variation in the host's developmental, metabolic, and immunological processes. This mutual process of epi- and microbiome remodeling could unfold across generations until the holobiont system has achieved a state of equilibrium (host-microbiome match). These ideas are central to the proposed "microbiome-epigenome-immunity axis" model presented next (Figure 1).

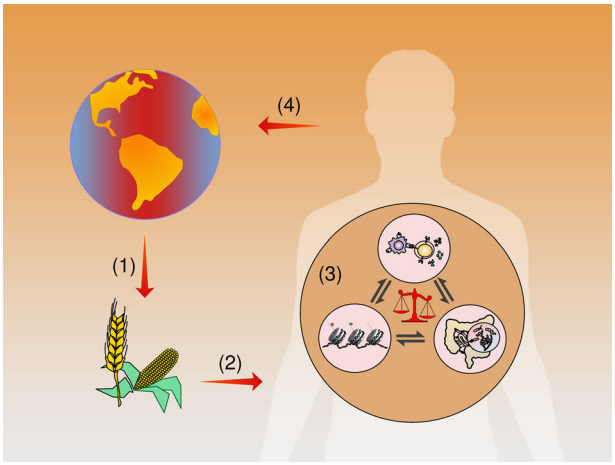

FIGURE 1 The holobiont's microbiome-epigenome-immunity axis. (1) Climate change alters human diets. (2) Climate change-related dietary shifts can shape the microbiome (e.g., influencing microbial diversity, composition or metabolites), the host's epigenome (e.g., through ingested compounds that modify gene expression), and the host immune systems (e.g., nutritional deficit can delay immune responses against pathogens). (3) Within the human holobiont the crosstalk between the microbiome, the host epigenome, and the host immune systems is extensive and dynamic. The host DNA and the environment influence this crosstalk (e.g., epigenetic factors flag the host niches for microbial colonization, a process that is also shaped by immune systems). Diet-mediated effects can knock the relationship between microbiome, epigenome, and immune systems off balance, with repercussions for holobiont traits, within and across generations. (4) Simultaneously, the human holobiont actively modifies its environment (e.g., through cultural niche construction) with potential downstream feedbacks

FROM DIETARY CHANGES TO ADAPTATION THROUGH DISEASE

Expanding on the foregoing propositions, we posit that the dominance and the recurrence of microbial species and their functions in humans[93] partly reflect conserved epigenetically-regulated processes that can transfer ecological information across generations. These epigenetic processes may guide the host's microbial colonization directly (e.g., through niche-specific gene regulation) and/or indirectly (e.g., through the plastic selectivity of the immune system[110]). The stability offered by the host's genome and socio-cultural context reinforces said epigenetic processes. We further posit that the "microbiome-epigenome-immunity axis" is sensitive to climate change-related shifts in diet, eating habits, and stress-related nutritional changes. Sufficient dietary changes alter the host epigenome and, by extension, the host microbiome. At the same time, they affect the process of microbial colonization and, through this, the host epigenome.

These dynamics generate varying levels of mismatch between the host's genetic makeup and its non-genetic components, thereby producing two key effects and trade-offs.

First, ecosystem services within the holobiont (see "From diet to phenotype through the microbiome") may be disrupted and harmful phenotypes may emerge. This aligns with the often-proposed link between abnormal gut microbiome composition and conditions such as obesity,[111] inflammatory bowel diseases,[112,113] and others.[114] However, dietary changes and anthropogenic effects that alter the resident or colonizing microbiota (e.g., antibiotics) may also yield non-disease phenotypes. Previous studies suggest that a dysbiotic holobiont environment (i.e., one that engenders an imbalance in the composition and metabolic capacity of the microbiome) is associated with a reduced activity of the innate immune system in early life and the over-stimulation of the adaptive immune system (AIS) later in life.[115–117] On the one hand, AIS over-stimulation may enhance immunological misfiring, which facilitates the onset of autoimmune diseases.[115] On the other hand, AIS over-stimulation may potentiate the holobiont defense mechanisms, which normally deteriorate with age,[118] thereby extending the holobiont's lifespan. Moreover, the enhanced immunological misfiring that results from AIS over-stimulation is expected to lower the chances of carrying pregnancies to term.[119] For instance, the autoimmune disease systemic lupus erythematosus increases the risk of pregnancy loss, pre-term delivery, and placental insufficiency.[120,121] Thus, while increasing the risk of disorders, diet-related changes may also enhance longevity and reduce reproductive success in humans.

Second, the mismatch between the host's genetic makeup and its microbiome is likely to generate intra-holobiont stress, which may impose varying degrees of pressure on the holobiont components. This pressure, in our model, is analogous to that which unfolds in host-pathogen interactions or during biological invasions between native and invading species. Host-microbiome mismatch may, for example, trigger undesired immune responses, which weaken the host while simultaneously creating niche space for colonization after native (i.e., co-evolved) microbial components have been damaged. Thus, this mismatch represents a first step toward the acquisition of adaptive changes. To understand this evolutionary process it must first be noted that the mismatch between the host's genetic makeup and its microbiome can be inherited by successive generations. More specifically, the epigenome of dysbiotic holobionts might be passed from mother to fetus through direct transmission of the epigenetic modifications or by *de novo* induction of epigenetic marks.[122–124] These recurring epigenetic patterns favor the reconfiguration of the parental microbiome in the descendant holobionts (e.g.,[125]). This means that the descendants of individuals with autoimmune diseases are likely to display the same traits via non-genetic inheritance. Consistent with this, autoimmune disorders with modest heritability and shared environmental risk factors often recur across generations.[126,127] An implication of this model is that the positive correlation between parental and offspring lifespans in humans partly reflect *trans*-generational epigenetic inheritance, in line with previous observations,[128,129] and findings in other species.[130]

Compared to previous generation(s), the recurring physiological or immune response of descendant holobionts can be either attenuated or exacerbated depending on the level of mismatch between the host genes (half of which are inherited from the mother and half from the father) and the environment (which may be relatively constant or vary between generations). In a largely constant environment, inter-generational shifts in phenotypic traits may be directional and tend towards a local optimum. Alternatively, inter-generational shifts may be fluctuating and irregular when the environment continually changes. In the simplest case of a largely constant inter-generational environment and narrow genetic variability, the intra-holobiont stress facilitates the recovery of pre-dysbiosis relationships between life-history traits (i.e., reproductive success increases at the expense of longevity). More generally, we posit that there is a natural tendency for the mean fitness of a population to rebound upon health equilibrium disruption (Figure 2). Similar dynamics have been associated with "assisted gene flow," a practice by which suitable genotypes are relocated to help local populations to keep pace with climate change.[131] This relocation of nonlocal genotypes may result in outbreeding depression, which reduces a population's mean fitness relative to the parental population.[132,133] However, this reduction in fitness is most often temporary. The local population recovers within a few generations, possibly acquiring even higher mean fitness values than before the immigrant genotypes were introduced.[134]

RE-ESTABLISHING THE HOST-MICROBIOME EQUILIBRIUM

Epigenetic mechanisms that affect the inheritance of phenotypic states[34,135] can contribute to the establishment of optimal fitness in the new environment. Besides this, genetic changes that re-establish the host-microbiome harmonious relationship may also occur. Immunity, reproduction, and lifespan-related host genes underlie much of the plasticity discussed above. It follows that changes in these genes could help re-establish the pre-dysbiosis host-microbiome equilibrium. Indeed, these genes play a major role in human adaptation, being among the most frequent candidate targets of selection.[136–140]

Genetic changes may also accumulate in the microbial component of the holobiont. Stress-induced mutagenesis boosts mutation rates in microbes, accelerating the emergence of beneficial genetic variants.[141] Moreover, the rapid adaptation of the microbiome to stress (exposure to a toxic agent) and selection of resistant bacteria may enable the host's offspring to develop higher toxic tolerance,[142,143] which could be inherited though different channels of microbial transmission.[143,144] Finally, microbiome-driven adaptations to new diets may explain the consumption of seaweed in humans,[145] the evolution of herbivory in cows,[146] and sanguivory in vampire bats.[147] For example, it has been suggested that a substantial part of the morphological, immunological, and physiological adaptations necessary to cope with the new diet of vampire bats were not due to genomic adaptations in the host, but rather were driven by positive selection on genes in the functional core microbiome of com-

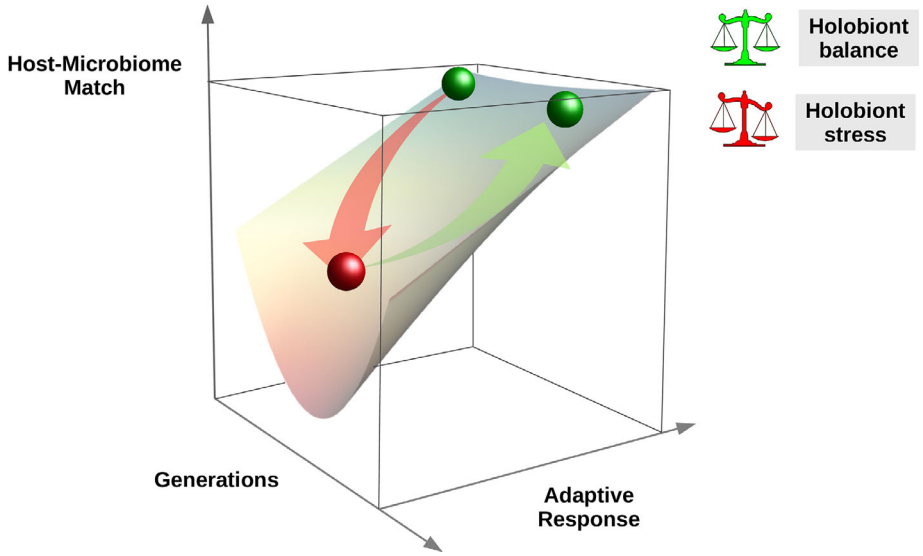

FIGURE 2 The holobiont's health and adaptation in response to dietary shifts. Dietary change triggers a host microbiome mismatch that perturbs the holobiont (e.g., triggering undesired immune responses in the host), while promoting its adaptive response (e.g., by creating niche space for novel microbial colonization). Arrows depict the evolutionary trajectory of human holobionts sparked by a climate change-induced dietary shift. Dietary change-related intra-holobiont stress is depicted in the first phase (red arrow). Here, holobionts face an increased susceptibility to illnesses, such as allergies and autoimmune diseases, which can be epigenetically inherited. In this perturbed health state, holobionts are subjected to pressures that promote the acquisition of microbial, genetic, and non-genetic variation, which eventually allows the holobionts to attain a new balance (green arrow)

mon bats.[147,148] Thus, thanks to the adaptive changes in their microbiome, holobionts may evolve adaptive solutions to nutritional challenges. Adaptive changes in the host genome may or may not accompany microbiome reconfigurations.

In sum, diet-related intra-holobiont stress may promote both genetic and non-genetic changes in the host and microbiome that may be transmitted to the next generation(s). While these changes may increase disease susceptibilities, they may also contribute to the re-alignment of host and microbiome interests. A re-established harmonious crosstalk between host and its microbiome (if achieved) signals the optimal integrated performance of the holobiont in the new environment (Figure 2).

MODEL IMPLICATIONS

The model presented above implies that host genes and microbiome may co-evolve and develop co-dependencies, consistent with a vast body of literature.[33,34,76,77,149] By integrating ecological, immunological, and evolutionary views on the holobiont, this model reconciles two seemingly distinct perspectives: the hologenome perspective, where the host and its microbiome evolve as a single cooperative unit of selection,[34,150,151] and a perspective that considers a host-microbiome system to be an ecological community[36,152] and an immunological individual.[153]

This integrative account extends the influential framework offered by the hologenome theory of evolution[76,150,154] in two significant ways. First, it makes novel predictions about evolutionary dynamics. Rather than assuming that rapid changes in the microbiome could provide the host with the time necessary to adapt and evolve,[155] a process comparable to the Baldwin effect (see also[110]), our model predicts that the holobiont experiences short-term health struggles and a host-microbiome mismatch that must be solved. In other words, it points towards more complex dietary-induced evolutionary trajectories of the holobiont that occur at different time scales. It generates the testable hypothesis that the likelihood with which diseases emerge and the rapidity with which adaptation to the environment can be achieved scale positively with the levels of mismatch between the host's genetic background and the epigenetic and microbial changes. Differently put, high levels of stress may be both detrimental and beneficial for a population depending on which temporal scale the observer uses.

Second, our model expands the so-far largely gene-centered evolutionary view of holobionts—as hologenomes—through a focus on other levels of organization. This especially concerns the epigenome and the various non-genetic processes involved in the microbiome-epigenome-immunity axis. Through this broader perspective, the proposed model reconciles current and past views on the relative contribution of genetics, epigenetics, environmental change and stress to the biased production of adaptive variation (Box 2).

In addition to these expansions on the hologenome approach, this model provides an operational definition of "healthy" or "favorable" microbiome, that is, microbial consortia that are in harmony not only with the host's lifestyle and socio-cultural and environmental settings but, to a substantial part, as well with its genetic background. These consortia do not need to be composed of fixed species. Due to considerable metabolic redundancy, genes with the same function are distributed across many bacterial species. This allows a "healthy" gut microbiome to be assembled in many different ways, and allows for

Box 2. Biased variation in evolution

There are several explanations for how adaptive variation is produced in evolution (for a brief historical overview, see[156]). According to a widespread view, genetic variation is assumed to be impervious to environmental challenges, and therefore, to organismal prospects of adaptation. In this view, variation is random, gradual and slow. Another viewpoint is that variation is biased with respect to possible phenotypic outcomes.[157] The concept of developmental bias suggests that "perturbation (e.g., mutation, environmental change) to biological systems will tend to produce some variants more readily, or with higher probability than others".[158] Recently, the possibility of additional plasticity-led routes to adaptation, other than the widespread view of allelic replacement due to selection, has come to light.[159] Plasticity can be a first step in the emergence of heritable phenotypic variation through processes of "genetic assimilation," that is, across generations, plastic phenotypes can be reconstructed without a sustained environmental stimulus once their production is "canalized" through the acquisition of a genetic basis.[160–162] Until now, few biologists have considered the microbiome of developing organisms as a potential source for biased adaptive variation.[110,146,163] Our model points in that direction.

the loss or rediscovery of microbial taxa across host generations.[164] This definition could help implement optimal therapeutic strategies for "precision" gut microbiome modulation, which to date remain vague.[165]

The microbiome is often considered to be a fruitful target for therapeutic intervention of numerous chronic diseases, such as autoimmune diseases.[166,167] Provided that an altered microbiome is causally linked to a certain disease, forms of medical intervention that currently alleviate the health challenges associated with the focal disease are likely to mitigate or suppress the intra-holobiont stress. This, under our model, implies that medical intervention also delays the emergence of potentially adaptive variation. Qualitatively similar conclusions were drawn previously, based on the idea that medical intervention relaxes natural selection on disease-associated genetic variants.[168,169]

Finally, should our model be correct, then the current failure to account for the epigenetic-microbial context and inter-generational influences impede our understanding of many diseases. Specific genetic variants that are often associated with increased risk of, for example, cancer, might be significant only insofar as they are coupled with associated (micro)environmental factors.[170,171] This is important given the healthcare industry's rapid evolution. Patient-tailored treatments that follow a decontextualized identification and prediction of disease-susceptibility loci should be avoided unless non-genetic and environment-driven changes are also taken into account.

CONCLUSIONS

Until now few biologists have considered the microbiome of developing organisms as potential sources of biased and rapid adaptive variation,[110,146,163] particularly in humans. Here, we introduce a forward-looking model where the microbiome plays a role in the adaptation of modern human populations to environmental changes. We posit that dietary changes reconfigure epigenetically-controlled equilibrium health states in integrated human-microbiome collectives (holobionts). This reconfiguration is a double-edged sword. On the one hand, it may increase the risk and severity of diseases by modulating the expression of the holobiont's life-history traits, such as longevity and reproduction. On the other, it helps re-align the holobiont system with the new nutritional environment, leveraging the pressure that the mismatch between host's genes and microbiome generates. These hypothesized dynamics need not be exclusively coupled with ongoing climate change, nor must they apply exclusively to human holobionts. Rather, similar dynamics in the microbiome-epigenome-immunity axis may have occurred in response to past non-anthropogenic climate change and contributed to the evolutionary trajectory of our and other species.[172] To further explore the consequences of these ideas in humans, a closer look at the microbiome-epigenome-immunity axis is warranted. This axis connects two so-far insufficiently interlinked fields of research: human health and human evolution. In other words, we need to understand that the holobiont is both an immunological individual and an evolutionary individual. In order to study the complex entanglement of these two, we first need to grasp the limits and the scope of microbial variation in humans and to understand how widely and rapidly the (gut) microbial community can be restructured in the face of environmental change. A second challenge is to understand if (and if so, how) differences in gut microbial variability between and within human populations can lead to different health and evolutionary responses to climate change-related nutritional challenges. Finally, the development of patient-tailored medical applications should not view human individuals as the sole targets of climate change-related health interventions.[173] Instead, the collective of the holobiont should be considered a potential patient. Its complex internal interrelations, crosstalk, and tradeoffs need to become the focus of attention.

ACKNOWLEDGMENTS

The authors thank Azita Chellappoo, Guido Prieto, Florian Horn, and Franz Goller and two anonymous reviewers for constructive comments on earlier versions of this paper. The authors also would like to thank the DFG Research Training Group 2220 "Evolutionary Processes in Adaptation and Disease" at the University of Münster. This work was supported by the German Research Foundation (DFG), projects 281125614/GRK 2220 (F.C., V.V.) and BA 5808/2-1 (J.B., A.F.T.), and by the ERC Starting Grant 851004 (A.N.D.).

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Francesco Catania https://orcid.org/0000-0002-2652-9397
Jan Baedke https://orcid.org/0000-0003-2138-785X
Alejandro Fábregas-Tejeda https://orcid.org/0000-0002-1797-5467
Abigail Nieves Delgado https://orcid.org/0000-0002-5203-7222
Valerio Vitali https://orcid.org/0000-0003-3593-1510
Le Anh Nguyen Long https://orcid.org/0000-0002-6188-9646

REFERENCES

1. McMichael, A. J., Woodruff, R. E., & Hales, S. (2006). Climate change and human health: Present and future risks. *Lancet*, *367*(9513), 859–869. https://doi.org/10.1016/S0140-6736(06)68079-3
2. Meusel, D., Menne, B., Kirch, W., & Bertollini, R. (2004). Public health responses to extreme weather and climate events—A brief summary of the WHO meeting on this topic in Bratislava on 9–10 February 2004. *Journal of Public Health*, *12*(6), 371–381. https://doi.org/10.1007/s10389-004-0068-8.
3. Cheng, X., & Su, H. (2010). Effects of climatic temperature stress on cardiovascular diseases. *European Journal of Internal Medicine*, *21*(3), 164–167. https://doi.org/10.1016/j.ejim.2010.03.001
4. Ebi, K. L., & Bowen, K. (2016). Extreme events as sources of health vulnerability: Drought as an example. *Weather and Climate Extremes*, *11*, 95–102. https://doi.org/10.1016/j.wace.2015.10.001
5. Banwell, N., Rutherford, S., Mackey, B., Street, R., & Chu, C. (2018). Commonalities between disaster and climate change risks for health: A theoretical framework. *International Journal of Environmental Research and Public Health*, 15(3), 538. https://doi.org/10.3390/ijerph15030538
6. Dhankher, O. P., & Foyer, C. H. (2018). Climate resilient crops for improving global food security and safety. *Plant, Cell and Environment*, *41*(5), 877–884. https://doi.org/10.1111/pce.13207
7. Deutsch, C. A., Tewksbury, J. J., Tigchelaar, M., Battisti, D. S., Merrill, S. C., Huey, R. B., & Naylor, R. L. (2018). Increase in crop losses to insect pests in a warming climate. *Science*, *361*(6405), 916–919. https://doi.org/10.1126/science.aat3466
8. Yan, Y., Wang, Y. C., Feng, C. C., Wan, P. H. M., & Chang, K. T. T. (2017). Potential distributional changes of invasive crop pest species associated with global climate change. *Applied Geography*, *82*, 83–92. https://doi.org/10.1016/j.apgeog.2017.03.011.
9. Nielsen, A., Reitan, T., Rinvoll, A. W., & Brysting, A. K. (2017). Effects of competition and climate on a crop pollinator community. *Agriculture, Ecosystems & Environment*, *246*, 253–260. https://doi.org/10.1016/j.agee.2017.06.006.
10. Meldrum, G., Mijatović, D., Rojas, W., Flores, J., Pinto, M., Mamani, G., Condori, E., Hilaquita, D., Gruberg, H., & Padulosi, S. (2018). Climate change and crop diversity: Farmers' perceptions and adaptation on the Bolivian Altiplano. *Environment, Development and Sustainability*, *20*(2), 703–730. https://doi.org/10.1007/s10668-016-9906-4.
11. Alm, S., & Olsen, S. O. (2017). Coping with time pressure and stress: Consequences for families' food consumption. *Journal of Consumer Policy*, *40*(1), 105–123. https://doi.org/10.1007/s10603-016-9329-5.
12. Errisuriz, V. L., Pasch, K. E., & Perry, C. L. (2016). Perceived stress and dietary choices: The moderating role of stress management. *Eating Behaviors*, *22*, 211–216. https://doi.org/10.1016/j.eatbeh.2016.06.008
13. Bhat, M. I., & Kapila, R. (2017). Dietary metabolites derived from gut microbiota: Critical modulators of epigenetic changes in mammals. *Nutrition Reviews*, *75*(5), 374–389. https://doi.org/10.1093/nutrit/nux001
14. Tobi, E. W., Slieker, R. C., Luijk, R., Dekkers, K. F., Stein, A. D., Xu, K. M., Biobank-based Integrative Omics Studies, C., Slagboom, P. E., van Zwet, E. W., Lumey, L. H., & Heijmans, B. T. (2018). DNA methylation as a mediator of the association between prenatal adversity and risk factors for metabolic disease in adulthood. *Science Advances*, *4*(1), eaao4364. https://doi.org/10.1126/sciadv.aao4364
15. Lynch, J. B., & Hsiao, E. Y. (2019). Microbiomes as sources of emergent host phenotypes. *Science*, *365*(6460), 1405–1409. https://doi.org/10.1126/science.aay0240
16. Collens, A., Kelley, E., & Katz, L. A. (2019). The concept of the hologenome, an epigenetic phenomenon, challenges aspects of the modern evolutionary synthesis. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution*, *332*(8), 349–355. https://doi.org/10.1002/jez.b.22915
17. Herrera, M., Klein, S. G., Schmidt-Roach, S., Campana, S., Cziesielski, M. J., Chen, J. E., Duarte, C. M., & Aranda, M. (2020). Unfamiliar partnerships limit cnidarian holobiont acclimation to warming. *Global Change Biology*, *26*(10), 5539–5553. https://doi.org/10.1111/gcb.15263
18. Tomova, A., Bukovsky, I., Rembert, E., Yonas, W., Alwarith, J., Barnard, N. D., & Kahleova, H. (2019). The effects of vegetarian and vegan diets on gut microbiota. *Frontiers Nutrition 6*, 47. https://doi.org/10.3389/fnut.2019.00047
19. Lumey, L. H., Stein, A. D., & Susser, E. (2011). Prenatal famine and adult health. *Annual Review of Public Health*, *32*, 237–262. https://doi.org/10.1146/annurev-publhealth-031210-101230
20. Westendorp, R. G., & Kirkwood, T. B. (1998). Human longevity at the cost of reproductive success. *Nature*, *396*(6713), 743–746. https://doi.org/10.1038/25519
21. Aguilaniu, H. (2015). The mysterious relationship between reproduction and longevity. *Worm*, *4*(2), e1020276. https://doi.org/10.1080/21624054.2015.1020276
22. Wu, Z., Isik, M., Moroz, N., Steinbaugh, M. J., Zhang, P., & Blackwell, T. K. (2019). Dietary restriction extends lifespan through metabolic regulation of innate immunity. *Cell Metabolism*, *29*(5), 1192–1205 e8. https://doi.org/10.1016/j.cmet.2019.02.013
23. Kenyon, C. J. (2010). The genetics of ageing. *Nature*, *464*(7288), 504–512. https://doi.org/10.1038/nature08980
24. Taguchi, A., & White, M. F. (2008). Insulin-like signaling, nutrient homeostasis, and life span. *Annual Review of Physiology*, *70*, 191–212. https://doi.org/10.1146/annurev.physiol.70.113006.100533
25. Fontana, L., & Partridge, L. (2015). Promoting health and longevity through diet: From model organisms to humans. *Cell*, *161*(1), 106–118. https://doi.org/10.1016/j.cell.2015.02.020
26. Arking, R. (2019). *Biology of longevity and aging. Pathways and Prospects.* (4th ed.). Oxford University Press.
27. Roseboom, T., de Rooij, S., & Painter, R. (2006). The Dutch famine and its long-term consequences for adult health. *Early Human Development*, *82*(8), 485–491. https://doi.org/10.1016/j.earlhumdev.2006.07.001
28. Bourke, C. D., Berkley, J. A., & Prendergast, A. J. (2016). Immune dysfunction as a cause and consequence of malnutrition. *Trends in Immunology*, *37*(6), 386–398. https://doi.org/10.1016/j.it.2016.04.003
29. Grueber, C. E., Gray, L. J., Morris, K. M., Simpson, S. J., & Senior, A. M. (2018). Intergenerational effects of nutrition on immunity: A systematic review and meta-analysis. *Biological Reviews of the Cambridge Philosophical Society*, *93*(2), 1108–1124. https://doi.org/10.1111/brv.12387
30. Kaati, G., Bygren, L. O., & Edvinsson, S. (2002). Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. *European Journal of Human Genetics*, *10*(11), 682–688. https://doi.org/10.1038/sj.ejhg.5200859

31. Ochoa-Hueso, R. (2017). Global change and the soil microbiome: A human-health perspective. *Frontiers in Ecology and Evolution*, *5*, 71. https://doi.org/10.3389/fevo.2017.00071.
32. Baedke, J., Fábregas-Tejeda, A., & Nieves Delgado, A. (2020). The holobiont concept before Margulis. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution*, *334*(3), 149–155. https://doi.org/10.1002/jez.b.22931
33. Bordenstein, S. R., & Theis, K. R. (2015). Host biology in light of the microbiome: Ten principles of holobionts and hologenomes. *Plos Biology*, 13(8), e1002226. ARTN https://doi.org/10.1371/journal.pbio.1002226
34. Gilbert, S. F., Sapp, J., & Tauber, A. I. (2012). A symbiotic view of life: We have never been individuals. *Quarterly Review of Biology*, *87*(4), 325–341. https://doi.org/10.1086/668166
35. Rosenberg, E., & Zilber-Rosenberg, I. (2016). Microbes drive evolution of animals and plants: The hologenome concept. *MBio*, *7*(2), e01395. https://doi.org/10.1128/mBio.01395-15
36. Suárez, J., & Stencel, A. (2020). A part-dependent account of biological individuality: Why holobionts are individuals and ecosystems simultaneously. *Biological Reviews*, *95*(5), 1308–1324. https://doi.org/10.1111/brv.12610
37. Burkhard, B., & Maes, J. (2017). *Mapping ecosystem services*. Pensoft Publishers. https://doi.org/10.3897/ab.e12837.
38. Thaiss, C. A., Zmora, N., Levy, M., & Elinav, E. (2016). The microbiome and innate immunity. *Nature*, *535*(7610), 65–74. https://doi.org/10.1038/nature18847
39. Chow, J., Lee, S. M., Shen, Y., Khosravi, A., & Mazmanian, S. K. (2010). Host-bacterial symbiosis in health and disease. *Advances in Immunology*, *107*, 243–274. https://doi.org/10.1016/B978-0-12-381300-8.00008-3
40. Belkaid, Y., & Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. *Cell*, *157*(1), 121–141. https://doi.org/10.1016/j.cell.2014.03.011
41. Sampson, T. R., Debelius, J. W., Thron, T., Janssen, S., Shastri, G. G., Ilhan, Z. E., Challis, C., Schretter, C. E., Rocha, S., Gradinaru, V., Chesselet, M. F., Keshavarzian, A., Shannon, K. M., Krajmalnik-Brown, R., Wittung-Stafshede, P., Knight, R., & Mazmanian, S. K. (2016). Gut Microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell*, *167*(6), 1469–1480 e12. https://doi.org/10.1016/j.cell.2016.11.018
42. Hsiao, E. Y., McBride, S. W., Hsien, S., Sharon, G., Hyde, E. R., McCue, T., Codelli, J. A., Chow, J., Reisman, S. E., Petrosino, J. F., Patterson, P. H., & Mazmanian, S. K. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell*, *155*(7), 1451–1463. https://doi.org/10.1016/j.cell.2013.11.024
43. Forsythe, P., Kunze, W., & Bienenstock, J. (2016). Moody microbes or fecal phrenology: What do we know about the microbiota-gut-brain axis? *BMC Medicine*, *14*, 58. https://doi.org/10.1186/s12916-016-0604-8
44. LeBlanc, J. G., Milani, C., de Giori, G. S., Sesma, F., van Sinderen, D., & Ventura, M. (2013). Bacteria as vitamin suppliers to their host: A gut microbiota perspective. *Current Opinion in Biotechnology*, *24*(2), 160–168. https://doi.org/10.1016/j.copbio.2012.08.005
45. Cantarel, B. L., Lombard, V., & Henrissat, B. (2012). Complex carbohydrate utilization by the healthy human microbiome. *Plos One*, *7*(6), e28742. https://doi.org/10.1371/journal.pone.0028742
46. Macfarlane, S., & Macfarlane, G. T. (2003). Regulation of short-chain fatty acid production. *The Proceedings of the Nutrition Society*, *62*(1), 67–72. https://doi.org/10.1079/PNS2002207
47. Nakamura, N., Lin, H. C., McSweeney, C. S., Mackie, R. I., & Gaskins, H. R. (2010). Mechanisms of microbial hydrogen disposal in the human colon and implications for health and disease. *Annual Review of Food Science and Technology*, *1*, 363–395. https://doi.org/10.1146/annurev.food.102308.124101
48. Gibson, G. R., Macfarlane, G. T., & Cummings, J. H. (1993). Sulphate reducing bacteria and hydrogen metabolism in the human large intestine. *Gut*, *34*(4), 437–439. https://doi.org/10.1136/gut.34.4.437
49. Topping, D. L., & Clifton, P. M. (2001). Short-chain fatty acids and human colonic function: Roles of resistant starch and nonstarch polysaccharides. *Mitochondrial Membrane Permeabilization in Cell Death*, *81*(3), 1031–1064. https://doi.org/10.1152/physrev.2001.81.3.1031
50. Kreznar, J. H., Keller, M. P., Traeger, L. L., Rabaglia, M. E., Schueler, K. L., Stapleton, D. S., Zhao, W., Vivas, E. I., Yandell, B. S., Broman, A. T., Hagenbuch, B., Attie, A. D., & Rey, F. E. (2017). Host genotype and gut microbiome modulate insulin secretion and diet-induced metabolic phenotypes. *Cell Reports*, *18*(7), 1739–1750. https://doi.org/10.1016/j.celrep.2017.01.062
51. Rothschild, D., Weissbrod, O., Barkan, E., Kurilshikov, A., Korem, T., Zeevi, D., Costea, P. I., Godneva, A., Kalka, I. N., Bar, N., Shilo, S., Lador, D., Vila, A. V, Zmora, N., Pevsner-Fischer, M., Israeli, D., Kosower, N., Malka, G., Wolf, B. C., … Segal, E. (2018). Environment dominates over host genetics in shaping human gut microbiota. *Nature*, *555*(7695), 210–215. https://doi.org/10.1038/nature25973
52. Zhernakova, A., Kurilshikov, A., Bonder, M. J., Tigchelaar, E. F., Schirmer, M., Vatanen, T., Mujagic, Z., Vila, A. V, Falony, G., Vieira-Silva, S., Wang, J., Imhann, F., Brandsma, E., Jankipersadsing, S. A., Joossens, M., Cenit, M. C., Deelen, P., Swertz, M. A., LifeLines cohort, study, … Fu, J. (2016). Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science*, *352*(6285), 565–569. https://doi.org/10.1126/science.aad3369
53. Kolodziejczyk, A. A., Zheng, D., & Elinav, E. (2019). Diet-microbiota interactions and personalized nutrition. *Nature Reviews Microbiology*, *17*(12), 742–753. https://doi.org/10.1038/s41579-019-0256-8
54. Schnorr, S. L., Candela, M., Rampelli, S., Centanni, M., Consolandi, C., Basaglia, G., Turroni, S., Biagi, E., Peano, C., Severgnini, M., Fiori, J., Gotti, R., De Bellis, G., Luiselli, D., Brigidi, P., Mabulla, A., Marlowe, F., Henry, A. G., & Crittenden, A. N. (2014). Gut microbiome of the Hadza hunter-gatherers. *Nature Communications*, *5*, 3654. https://doi.org/10.1038/ncomms4654
55. Bright, M., & Bulgheresi, S. (2010). A complex journey: Transmission of microbial symbionts. *Nature Reviews Microbiology*, *8*(3), 218–230. https://doi.org/10.1038/nrmicro2262
56. Funkhouser, L. J., & Bordenstein, S. R. (2013). Mom knows best: The universality of maternal microbial transmission. *Plos Biology*, 11(8), e1001631. ARTN https://doi.org/10.1371/journal.pbio.1001631
57. Muegge, B. D., Kuczynski, J., Knights, D., Clemente, J. C., González, A., Fontana, L., Henrissat, B., Knight, R., & Gordon, J. I. (2011). Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science*, *332*, 970–974. https://doi.org/10.1126/science.1198719
58. Stencel, A. (2021). Do seasonal microbiome changes affect infection susceptibility, contributing to seasonal disease outbreaks? *Bioessays*, *43*(1), 2000148. https://doi.org/10.1002/bies.202000148
59. Blaser, M. J., & Falkow, S. (2009). What are the consequences of the disappearing human microbiota? *Nature Reviews Microbiology*, *7*(12), 887–894. https://doi.org/10.1038/nrmicro2245
60. Wang, B., Yao, M., Lv, L., Ling, Z., & Li, L. (2017). The human microbiota in health and disease. *Engineering*, *3*(1), 71–82. https://doi.org/10.1016/J.ENG.2017.01.008
61. Zmora, N., Suez, J., & Elinav, E. (2019). You are what you eat: Diet, health and the gut microbiota. *Nature Reviews Gastroenterology & Hepatology*, *16*(1), 35–56. https://doi.org/10.1038/s41575-018-0061-2
62. Li, B., Selmi, C., Tang, R., Gershwin, M. E., & Ma, X. (2018). The microbiome and autoimmunity: A paradigm from the gut-liver axis. *Cellular & Molecular Immunology*, *15*(6), 595–609. https://doi.org/10.1038/cmi.2018.7

63. Seo, D. O., & Holtzman, D. M. (2020). Gut microbiota: From the forgotten organ to a potential key player in the pathology of Alzheimer's disease. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *75*(7), 1232–1241. https://doi.org/10.1093/gerona/glz262
64. Vangoitsenhoven, R., & Cresci, G. A. M. (2020). Role of microbiome and antibiotics in autoimmune diseases. *Nutrition in Clinical Practice*, *35*(3), 406–416. https://doi.org/10.1002/ncp.10489
65. Wen, L., Ley, R. E., Volchkov, P. Y., Stranges, P. B., Avanesyan, L., Stonebraker, A. C., Hu, C., Wong, F. S., Szot, G. L., Bluestone, J. A., Gordon, J. I., & Chervonsky, A. V. (2008). Innate immunity and intestinal microbiota in the development of Type 1 diabetes. *Nature*, *455*(7216), 1109–1113. https://doi.org/10.1038/nature07336
66. Schwabe, R. F., & Jobin, C. (2013). The microbiome and cancer. *Nature Reviews Cancer*, *13*(11), 800–812. https://doi.org/10.1038/nrc3610
67. Al-Assal, K., Martinez, A. C., Torrinhas, R. S., Cardinelli, C., & Waitzberg, D. (2018). Gut microbiota and obesity. *Clinical Nutrition Experimental*, *20*, 60–64. https://doi.org/10.1016/j.yclnex.2018.03.001
68. Valles-Colomer, M., Falony, G., Darzi, Y., Tigchelaar, E. F., Wang, J., Tito, R. Y., Schiweck, C., Kurilshikov, A., Joossens, M., Wijmenga, C., Claes, S., Van Oudenhove, L., Zhernakova, A., Vieira-Silva, S., & Raes, J. (2019). The neuroactive potential of the human gut microbiota in quality of life and depression. *Nature Microbiology*, *4*(4), 623–632. https://doi.org/10.1038/s41564-018-0337-x
69. Fischbach, M. A. (2018). Microbiome: Focus on causation and mechanism. *Cell*, *174*(4), 785–790. https://doi.org/10.1016/j.cell.2018.07.038
70. Koskella, B., Hall, L. J., & Metcalf, C. J. E. (2017). The microbiome beyond the horizon of ecological and evolutionary theory. *Nature Ecology & Evolution*, *1*(11), 1606–1615. https://doi.org/10.1038/s41559-017-0340-2
71. Zeng, Q., Sukumaran, J., Wu, S., & Rodrigo, A. (2015). Neutral models of microbiome evolution. *PLoS Computational Biology*, *11*(7), e1004365. https://doi.org/10.1371/journal.pcbi.1004365
72. Zeng, Q., Wu, S., Sukumaran, J., & Rodrigo, A. (2017). Models of microbiome evolution incorporating host and microbial selection. *Microbiome*, *5*(1), 127. https://doi.org/10.1186/s40168-017-0343-x
73. Huitzil, S., Sandoval-Motta, S., Frank, A., & Aldana, M. (2018). Modeling the role of the microbiome in evolution. *Frontiers in Physiology*, *9*, 1836. https://doi.org/10.3389/fphys.2018.01836
74. Suárez, J. (2020). The stability of traits conception of the hologenome: An evolutionary account of holobiont individuality. *History and Philosophy of the Life Sciences*, *42*(1), 11. https://doi.org/10.1007/s40656-020-00305-2
75. Bapteste, E., & Papale, F. (2021). Modeling the evolution of interconnected processes: It is the song and the singers. *Bioessays*, *43*(1), 2000077. https://doi.org/10.1002/bies.202000077
76. Rosenberg, E., & Zilber-Rosenberg, I. (2018). The hologenome concept of evolution after 10 years. *Microbiome*, *6*, 78. https://doi.org/10.1186/s40168-018-0457-9
77. Roughgarden, J. (2020). Holobiont evolution: Mathematical model with vertical vs. horizontal microbiome transmission. *Philosophy, Theory, and Practice in Biology*, *12*(002), ISSN 2475–3025. https://doi.org/10.3998/ptpbio.16039257.0012.002
78. Eckburg, P. B., Bik, E. M., Bernstein, C. N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S. R., Nelson, K. E., & Relman, D. A. (2005). Diversity of the human intestinal microbial flora. *Science*, *308*(5728), 1635–1638. https://doi.org/10.1126/science.1110591
79. Gill, S. R., Pop, M., Deboy, R. T., Eckburg, P. B., Turnbaugh, P. J., Samuel, B. S., Gordon, J. I., Relman, D. A., Fraser-Liggett, C. M., & Nelson, K. E. (2006). Metagenomic analysis of the human distal gut microbiome. *Science*, *312*(5778), 1355–1359. https://doi.org/10.1126/science.1124234
80. Pei, Z., Bini, E. J., Yang, L., Zhou, M., Francois, F., & Blaser, M. J. (2004). Bacterial biota in the human distal esophagus. *PNAS*, *101*(12), 4250–4255. https://doi.org/10.1073/pnas.0306398101
81. Aas, J. A., Paster, B. J., Stokes, L. N., Olsen, I., & Dewhirst, F. E. (2005). Defining the normal bacterial flora of the oral cavity. *Journal of Clinical Microbiology*, *43*(11), 5721–5732. https://doi.org/10.1128/JCM.43.11.5721-5732.2005
82. Gao, Z., Tseng, C. H., Pei, Z., & Blaser, M. J. (2007). Molecular analysis of human forearm superficial skin bacterial biota. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(8), 2927–2932. https://doi.org/10.1073/pnas.0607077104
83. Bik, E. M., Eckburg, P. B., Gill, S. R., Nelson, K. E., Purdom, E. A., Francois, F., Perez-Perez, G., Blaser, M. J., & Relman, D. A. (2006). Molecular analysis of the bacterial microbiota in the human stomach. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(3), 732–737. https://doi.org/10.1073/pnas.0506655103
84. Moeller, A. H., Li, Y., Ngole, E. M., Ahuka-Mundeke, S., Lonsdorf, E. V, Pusey, A. E., Peeters, M., Hahn, B. H., & Ochman, H. (1419). Rapid changes in the gut microbiome during human evolution. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(46), 16431–16435. https://doi.org/10.1073/pnas.1419136111
85. Lloyd, E. A., & Wade, M. J. (2019). Criteria for holobionts from community genetics. *Biological Theory*, *14*(3), 151–170. https://doi.org/10.1007/s13752-019-00322-w
86. Fisher, R. M., Henry, L. M., Cornwallis, C. K., Kiers, E. T., & West, S. A. (2017). The evolution of host-symbiont dependence. *Nature Communications*, *8*(1), 1–8. https://doi.org/10.1038/ncomms15973
87. Gomez de Aguero, M., Ganal-Vonarburg, S. C., Fuhrer, T., Rupp, S., Uchimura, Y., Li, H., Steinert, A., Heikenwalder, M., Hapfelmeier, S., Sauer, U., McCoy, K. D., & Macpherson, A. J. (2016). The maternal microbiota drives early postnatal innate immune development. *Science*, *351*(6279), 1296–1302. https://doi.org/10.1126/science.aad2571
88. Koenig, J. E., Spor, A., Scalfone, N., Fricker, A. D., Stombaugh, J., Knight, R., Angenent, L. T., & Ley, R. E. (2011). Succession of microbial consortia in the developing infant gut microbiome. *Proceedings of the National Academy of Sciences of the United States of America*, *108 Suppl*, 4578–4585. https://doi.org/10.1073/pnas.1000081107
89. Yatsunenko, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras, M., Magris, M., Hidalgo, G., Baldassano, R. N., Anokhin, A. P., Heath, A. C., Warner, B., Reeder, J., Kuczynski, J., Caporaso, J. G., Lozupone, C. A., Lauber, C., Clemente, J. C., Knights, D., … Gordon, J. I. (2012). Human gut microbiome viewed across age and geography. *Nature*, *486*(7402), 222–227. https://doi.org/10.1038/nature11053
90. Goodrich, J. K., Waters, J. L., Poole, A. C., Sutter, J. L., Koren, O., Blekhman, R., Beaumont, M., Van Treuren, W., Knight, R., Bell, J. T., Spector, T. D., Clark, A. G., & Ley, R. E. (2014). Human genetics shape the gut microbiome. *Cell*, *159*(4), 789–799. https://doi.org/10.1016/j.cell.2014.09.053
91. Fierer, N., Hamady, M., Lauber, C. L., & Knight, R. (2008). The influence of sex, handedness, and washing on the diversity of hand surface bacteria. *PNAS*, *105*(46), 17994–17999. https://doi.org/10.1073/pnas.0807920105
92. Human Microbiome Project, C. (2012). Structure, function and diversity of the healthy human microbiome. *Nature*, *486*(7402), 207–214. https://doi.org/10.1038/nature11234
93. Turnbaugh, P. J., Hamady, M., Yatsunenko, T., Cantarel, B. L., Duncan, A., Ley, R. E., Sogin, M. L., Jones, W. J., Roe, B. A., Affourtit, J. P., Egholm, M., Henrissat, B., Heath, A. C., Knight, R., & Gordon, J. I. (2009). A core gut microbiome in obese and lean twins. *Nature*, *457*(7228), 480–484. https://doi.org/10.1038/nature07540
94. Gilbert, S. F. (2014). A holobiont birth narrative: The epigenetic transmission of the human microbiome. *Frontiers in Genetics*, *5*, 282. https://doi.org/10.3389/fgene.2014.00282
95. Li, W., Tapiainen, T., Brinkac, L., Lorenzi, H. A., Moncera, K., Tejesvi, M., Salo, J., & Nelson, K. E. (2020). Vertical transmission of gut

microbiome and antimicrobial resistance genes in infants exposed to antibiotics at birth. *Journal of Infectious Diseases*, jiaa155. https://doi.org/10.1093/infdis/jiaa155

96. Quin, C., & Gibson, D. L. (2020). Human behavior, not race or geography, is the strongest predictor of microbial succession in the gut bacteriome of infants. *Gut Microbes*, *11*(5), 1143–1171. https://doi.org/10.1080/19490976.2020.1736973
97. Sarkar, A., Harty, S., Johnson, K. V.-A., Moeller, A. H., Archie, E. A., Schell, L. D., Carmody, R. N., Clutton-Brock, T. H., Dunbar, R. I. M., & Burnet, P. W. J. (2020). Microbial transmission in animal social networks and the social microbiome. *Nature Ecology & Evolution*, *4*(8), 1020–1035. https://doi.org/10.1038/s41559-020-1220-8
98. Tung, J., Barreiro, L. B., Burns, M. B., Grenier, J. C., Lynch, J., Grieneisen, L. E., Altmann, J., Alberts, S. C., Blekhman, R., & Archie, E. A. (2015). Social networks predict gut microbiome composition in wild baboons. *ELife*, 2015(4). https://doi.org/10.7554/eLife.05224
99. Finlay, B. B. (2020). Are noncommunicable diseases communicable? *Science*, *367*(6475), 250–251. https://doi.org/10.1126/science.aaz3834
100. Spor, A., Koren, O., & Ley, R. (2011). Unravelling the effects of the environment and host genotype on the gut microbiome. *Nature Reviews Microbiology*, *9*(4), 279–290. https://doi.org/10.1038/nrmicro2540
101. Knights, D., Silverberg, M. S., Weersma, R. K., Gevers, D., Dijkstra, G., Huang, H., Tyler, A. D., van Sommeren, S., Imhann, F., Stempak, J. M., Huang, H., Vangay, P., Al-Ghalith, G. A., Russell, C., Sauk, J., Knight, J., Daly, M. J., Huttenhower, C., & Xavier, R. J. (2014). Complex host genetics influence the microbiome in inflammatory bowel disease. *Genome Medicine*, *6*(12), 107. https://doi.org/10.1186/s13073-014-0107-1
102. Benson, A. K., Kelly, S. A., Legge, R., Ma, F., Low, S. J., Kim, J., Zhang, M., Oh, P. L., Nehrenberg, D., Hua, K., Kachman, S. D., Moriyama, E. N., Walter, J., Peterson, D. A., & Pomp, D. (2010). Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors. *Proceedings of the National Academy of Sciences*, *107*(44), 18933–18938. https://doi.org/10.1073/pnas.1007028107
103. Cavalli, G., & Heard, E. (2019). Advances in epigenetics link genetics to the environment and disease. *Nature*, *571*(7766), 489–499. https://doi.org/10.1038/s41586-019-1411-0
104. Miro-Blanch, J., & Yanes, O. (2019). Epigenetic Regulation at the interplay between gut microbiota and host metabolism. *Frontiers in Genetics*, *10*, 638. https://doi.org/10.3389/fgene.2019.00638
105. Sharma, M., Li, Y., Stoll, M. L., & Tollefsbol, T. O. (2020). The epigenetic connection between the gut microbiome in obesity and diabetes. *Frontiers in Genetics*, *10*, 1329. https://doi.org/10.3389/fgene.2019.01329
106. Lee, H.-S. (2019). The interaction between gut microbiome and nutrients on development of human disease through epigenetic mechanisms. *Genomics & Informatics*, *17*(3), e24. https://doi.org/10.5808/GI.2019.17.3.e24
107. Breton, J., Tennoune, N., Lucas, N., Francois, M., Legrand, R., Jacquemot, J., Goichon, A., Guérin, C., Peltier, J., Pestel-Caron, M., Chan, P., Vaudry, D., Do Rego, J. C., Liénard, F., Pénicaud, L., Fioramonti, X., Ebenezer, I. S., Hökfelt, T., Déchelotte, P., & Fetissov, S. O. (2016). Gut commensal *E. coli* proteins activate host satiety pathways following nutrient-induced bacterial growth. *Cell Metabolism*, *23*(2), 324–334. https://doi.org/10.1016/j.cmet.2015.10.017
108. Groves, H. T., Higham, S. L., Moffatt, M. F., Cox, M. J., & Tregoning, J. S. (2020). Respiratory viral infection alters the gut microbiota by inducing inappetence. *MBio*, *11*(1), e03236-19. https://doi.org/10.1128/mBio.03236-19
109. Jasiulionis, M. G. (2018). Abnormal epigenetic regulation of immune system during aging. *Frontiers in Immunology*, *9*, 197. https://doi.org/10.3389/fimmu.2018.00197
110. Kolodny, O., & Schulenburg, H. (2020). Microbiome-mediated plasticity directs host evolution along several distinct time scales. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *375*(1808), 20190589. https://doi.org/10.1098/rstb.2019.0589
111. Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, *444*(7122), 1027–1031. https://doi.org/10.1038/nature05414
112. Lucas López, R., Grande Burgos, M. J., Gálvez, A., & Pérez Pulido, R. (2017). The human gastrointestinal tract and oral microbiota in inflammatory bowel disease: A state of the science review. *Apmis*, *125*(1), 3–10. https://doi.org/10.1111/apm.12609
113. Smith, P. M., Howitt, M. R., Panikov, N., Michaud, M., Gallini, C. A., Bohlooly-Y, M., Glickman, J. N., & Garrett, W. S. (2013). The microbial metabolites, short-chain fatty acids, regulate colonic T reg cell homeostasis. *Science*, *341*(6145), 569–573. https://doi.org/10.1126/science.1241165
114. Singh, R. K., Chang, H. W., Yan, D., Lee, K. M., Ucmak, D., Wong, K., Abrouk, M., Farahnik, B., Nakamura, M., Zhu, T. H., Bhutani, T., & Liao, W. (2017). Influence of diet on the gut microbiome and implications for human health. *Journal of Translational Medicine*, *15*(1), 73. https://doi.org/10.1186/s12967-017-1175-y
115. Bayersdorf, R., Fruscalzo, A., & Catania, F. (2018). Linking autoimmunity to the origin of the adaptive immune system. *Evolution, Medicine, and Public HEALTH*, *2018*(1), 2–12. https://doi.org/10.1093/emph/eoy001
116. Torres, J., Hu, J., Seki, A., Eisele, C., Nair, N., Huang, R., Tarassishin, L., Jharap, B., Cote-Daigneault, J., Mao, Q., Mogno, I., Britton, G. J., Uzzan, M., Chen, C. L., Kornbluth, A., George, J., Legnani, P., Maser, E., Loudon, H., … Peter, I. (2020). Infants born to mothers with IBD present with altered gut microbiome that transfers abnormalities of the adaptive immune system to germ-free mice. *Gut*, *69*(1), 42–51. https://doi.org/10.1136/gutjnl-2018-317855
117. Al Nabhani, Z., & Eberl, G. (2020). Imprinting of the immune system by the microbiota early in life. *Mucosal Immunology*, *13*(2), 183–189. https://doi.org/10.1038/s41385-020-0257-y
118. Weng, N. ping. (2006). Aging of the immune system: How much can the adaptive immune system adapt? *Immunity*, *24*(5), 495–499. https://doi.org/10.1016/j.immuni.2006.05.001
119. Lorenz, T. K., Worthman, C. M., & Vitzthum, V. J. (2015). Links among inflammation, sexual activity and ovulation: Evolutionary trade-offs and clinical implications. *Evolution, Medicine, and Public Health*, *2015*(1), 304–324. https://doi.org/10.1093/emph/eov029
120. Hayslett, J. P. (1992). The effect of systemic lupus erythematosus on pregnancy and pregnancy outcome. *American Journal of Reproductive Immunology*, *28*(3–4), 199–204. https://doi.org/10.1111/j.1600-0897.1992.tb00791.x
121. Pastore, D. E. A., Costa, M. L., & Surita, F. G. (2019). Systemic lupus erythematosus and pregnancy: The challenge of improving antenatal care and outcomes. *Lupus*, *28*(12), 1417–1426. https://doi.org/10.1177/0961203319877247
122. Burdge, G. C., Hoile, S. P., Uller, T., Thomas, N. A., Gluckman, P. D., Hanson, M. A., & Lillycrop, K. A. (2011). Progressive, transgenerational changes in offspring phenotype and epigenotype following nutritional transition. *Plos One*, *6*(11), e28282. https://doi.org/10.1371/journal.pone.0028282
123. Schulfer, A. F., Battaglia, T., Alvarez, Y., Bijnens, L., Ruiz, V. E., Ho, M., Robinson, S., Ward, T., Cox, L. M., Rogers, A. B., Knights, D., Sartor, R. B., & Blaser, M. J. (2018). Intergenerational transfer of antibiotic-perturbed microbiota enhances colitis in susceptible mice. *Nature Microbiology*, *3*(2), 234–242. https://doi.org/10.1038/s41564-017-0075-5
124. Ma, J., Prince, A. L., Bader, D., Hu, M., Ganu, R., Baquero, K., Blundell, P., Alan Harris, R., Frias, A. E., Grove, K. L., & Aagaard, K. M.

(2014). High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model. *Nature Communications*, *5*, 3889. https://doi.org/10.1038/ncomms4889

125. Vangay, P., Johnson, A. J., Ward, T. L., Al-Ghalith, G. A., Shields-Cutler, R. R., Hillmann, B. M., Lucas, S. K., Beura, L. K., Thompson, E. A., Till, L. M., Batres, R., Paw, B., Pergament, S. L., Saenyakul, P., Xiong, M., Kim, A. D., Kim, G., Masopust, D., Martens, E. C., … Knights, D. (2018). US immigration westernizes the human gut microbiome. *Cell*, *175*(4), 962–972 e10. https://doi.org/10.1016/j.cell.2018.10.029
126. Cho, J. H., & Feldman, M. (2015). Heterogeneity of autoimmune diseases: Pathophysiologic insights from genetics and implications for new therapies. *Nature Medicine*, *21*(7), 730–738. https://doi.org/10.1038/nm.3897
127. Selmi, C., Lu, Q., & Humble, M. C. (2012). Heritability versus the role of the environment in autoimmunity. *Journal of Autoimmunity*, *39*(4), 249–252. https://doi.org/10.1016/j.jaut.2012.07.011
128. Vågerö, D., Aronsson, V., & Modin, B. (2018). Why is parental lifespan linked to children's chances of reaching a high age? A transgenerational hypothesis. *SSM – Population Health*, *4*, 45–54. https://doi.org/10.1016/j.ssmph.2017.11.006
129. Kowald, A., & Kirkwood, T. B. L. (2016). Can aging be programmed? A critical literature review. *Aging Cell*, 15(6), 986–998. https://doi.org/10.1111/acel.12510
130. Greer, E. L., Maures, T. J., Ucar, D., Hauswirth, A. G., Mancini, E., Lim, J. P., Benayoun, B. A., Shi, Y., & Brunet, A. (2011). Transgenerational epigenetic inheritance of longevity in *Caenorhabditis elegans*. *Nature*, *479*(7373), 365–371. https://doi.org/10.1038/nature10572
131. Young, D. J. N., Blush, T. D., Landram, M., Wright, J. W., Latimer, A. M., & Safford, H. D. (2020). Assisted gene flow in the context of large-scale forest management in California, USA. *Ecosphere*, *11*(1), e03001. https://doi.org/10.1002/ecs2.3001
132. Edmands, S. (2007). Between a rock and a hard place: Evaluating the relative risks of inbreeding and outbreeding for conservation and management. *Molecular Ecology*, *16*, 463–475. https://doi.org/10.1111/j.1365-294X.2006.03148.x
133. Frankham, R., Ballou, J. D., Eldridge, M. D. B., Lacy, R. C., Ralls, K., Dudash, M. R., & Fenster, C. B. (2011). Predicting the probability of outbreeding depression. *Conservation Biology*, *25*(3), 465–475. https://doi.org/10.1111/j.1523-1739.2011.01662.x
134. Aitken, S. N., & Whitlock, M. C. (2013). Assisted gene flow to facilitate local adaptation to climate change. *Annual Review of Ecology, Evolution, and Systematics*, *44*, 13.1–13.22. https://doi.org/10.1146/annurev-ecolsys-110512-135747
135. Houri-Zeevi, L., Korem Kohanim, Y., Antonova, O., & Rechavi, O. (2020). Three rules explain transgenerational small RNA inheritance in *C. elegans*. *Cell*, *182*(5), 1186–1197.e12.https://doi.org/10.1016/j.cell.2020.07.022.
136. Pickrell, J. K., Coop, G., Novembre, J., Kudaravalli, S., Li, J. Z., Absher, D., Srinivasan, B. S., Barsh, G. S., Myers, R. M., Feldman, M. W., & Pritchard, J. K. (2009). Signals of recent positive selection in a worldwide sample of human populations. *Genome Research*, *19*(5), 826–837. https://doi.org/10.1101/gr.087577.108
137. Barreiro, L. B., Laval, G., Quach, H., Patin, E., & Quintana-Murci, L. (2008). Natural selection has driven population differentiation in modern humans. *Nature Genetics*, *40*(3), 340–345. https://doi.org/10.1038/ng.78
138. Fumagalli, M., Sironi, M., Pozzoli, U., Ferrer-Admetlla, A., Pattini, L., & Nielsen, R. (2011). Signatures of environmental genetic adaptation pinpoint pathogens as the main selective pressure through human evolution. *Plos Genetics*, *7*(11), e1002355. https://doi.org/10.1371/journal.pgen.1002355
139. Dapper, A. L., & Wade, M. J. (2020). Relaxed selection and the rapid evolution of reproductive genes. *Trends in Genetics*, *36*(9), 640–649. https://doi.org/10.1016/j.tig.2020.06.014
140. Sackton, T. B. (2020). Studying natural selection in the era of ubiquitous genomes. *Trends in Genetics*, *36*(10), 792–803. https://doi.org/10.1016/j.tig.2020.07.008
141. Fitzgerald, D. M., & Rosenberg, S. M. (2019). What is mutation? A chapter in the series: How microbes "jeopardize" the modern synthesis. *Plos Genetics*, *15*(4), e1007995. https://doi.org/10.1371/journal.pgen.1007995
142. Osmanovic, D., Kessler, D. A., Rabin, Y., & Soen, Y. (2018). Darwinian selection of host and bacteria supports emergence of Lamarckian-like adaptation of the system as a whole. *Biology Direct*, *13*(1), 24. https://doi.org/10.1186/s13062-018-0224-7
143. Wang, G. H., Berdy, B. M., Velasquez, O., Jovanovic, N., Alkhalifa, S., Minbiole, K. P. C., & Brucker, R. M. (2020). Changes in microbiome confer multigenerational host resistance after sub-toxic pesticide exposure. *Cell Host and Microbe*, *27*(2), 213–224.e7. https://doi.org/10.1016/j.chom.2020.01.009
144. Elgart, M., & Soen, Y. (2018). Microbiome-germline interactions and their transgenerational implications. *Bioessays*, *40*(4), e1700018. https://doi.org/10.1002/bies.201700018
145. Hehemann, J. H., Correc, G., Barbeyron, T., Helbert, W., Czjzek, M., & Michel, G. (2010). Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. *Nature*, *464*, 908–912. https://doi.org/10.1038/nature08937
146. Chiu, L., & Gilbert, S. F. (2020). 17 – Niche construction and the transition to herbivory: Phenotype switching and the organization of new nutritional modes. In H. Levine, M. K. Jolly, P. Kulkarni, & V. Nanjundiah (Eds.), *Phenotypic switching* (pp. 459–482). Academic Press. http://www.sciencedirect.com/science/article/pii/B9780128179963000153
147. Zepeda Mendoza, M. L., Xiong, Z., Escalera-Zamudio, M., Runge, A. K., Thézé, J., Streicker, D., Frank, H. K., Loza-Rubio, E., Liu, S., Ryder, O. A., Samaniego Castruita, J. A., Katzourakis, A., Pacheco, G., Taboada, B., Löber, U., Pybus, O. G., Li, Y., Rojas-Anaya, E., Bohmann, K., … Gilbert, M. P. T. (2018). Hologenomic adaptations underlying the evolution of sanguivory in the common vampire bat. *Nature Ecology & Evolution*, *2*(4), 659–668. https://doi.org/10.1038/s41559-018-0476-8
148. Suárez, J., & Triviño, V. (2020). What is a hologenomic adaptation? Emergent individuality and inter-identity in multispecies systems. *Frontiers in Psychology*, *11*, 187. https://doi.org/10.3389/fpsyg.2020.00187
149. Roughgarden, J., Gilbert, S. F., Rosenberg, E., Zilber-Rosenberg, I., & Lloyd, E. A. (2018). Holobionts as units of selection and a model of their population dynamics and evolution. *Biological Theory*, *13*(1), 44–65. https://doi.org/10.1007/s13752-017-0287-1
150. Zilber-Rosenberg, I., & Rosenberg, E. (2008). Role of microorganisms in the evolution of animals and plants: The hologenome theory of evolution. *Fems Microbiology Reviews*, *32*(5), 723–735. https://doi.org/10.1111/j.1574-6976.2008.00123.x
151. Rosenberg, E., & Zilber-Rosenberg, I. (2013). *The Hologenome Concept: Human, Animal and Plant Microbiota*. Springer.
152. Douglas, A. E., & Werren, J. H. (2016). Holes in the hologenome: Why host-microbe symbioses are not holobionts. *MBio*, *7*(2), e02099-15. https://doi.org/10.1128/mBio.02099-15
153. Pradeu, T. (2016). Organisms or biological individuals? Combining physiological and evolutionary individuality. *Biology and Philosophy*, *31*, 797–817. https://doi.org/10.1007/s10539-016-9551-1
154. Rosenberg, E., & Zilber-Rosenberg, I. (2019). The hologenome concept of evolution: Medical implications. *Rambam Maimonides Medical Journal*, *10*(1), e0005. https://doi.org/10.5041/RMMJ.10359
155. Rosenberg, E., & Zilber-Rosenberg, I. (2011). Symbiosis and development: The hologenome concept. *Birth Defects Research Part C – Embryo Today: Reviews*, *93*(1), 56–66. https://doi.org/10.1002/bdrc.20196
156. Bowler, P. J. (2005). CHAPTER 2 – Variation from Darwin to the modern synthesis. In B. Hallgrímsson & B. K. Hall (Eds.), *Variation*

(pp. 9–27). Academic Press. http://www.sciencedirect.com/science/article/pii/B9780120887774500041
157. Smith, J. M., Burian, R., Kauffman, S., Alberch, P., Campbell, J., Goodwin, B., Lande, R., Raup, D., & Wolpert, L. (1985). Developmental constraints and evolution: A perspective from the Mountain Lake Conference on Development and Evolution. *The Quarterly Review of Biology*, *60*(3), 265–287. https://doi.org/10.1086/414425
158. Uller, T., Moczek, A. P., Watson, R. A., Brakefield, P. M., & Laland, K. N. (2018). Developmental bias and evolution: A regulatory network perspective. *Genetics*, *209*(4), 949–966. https://doi.org/10.1534/genetics.118.300995
159. West-Eberhard, M. J. (2003). *Developmental plasticity and evolution*. Oxford University Press.
160. Waddington, C. H. (1942). Canalization of development and the inheritance of acquired characters. *Nature*, *150*(3811), 563–565. https://doi.org/10.1038/150563a0
161. Waddington, C. H. (1953). Genetic assimilation of an acquired character. *Evolution; International Journal of Organic Evolution*, *7*, 118–126. https://doi.org/10.1111/j.1558-5646.1953.tb00070.x.
162. Waddington, C. H. (1956). Genetic assimilation of the bithorax phenotype. *Evolution; International Journal of Organic Evolution*, *10*(1), 1–13. https://doi.org/10.2307/2406091.
163. Voolstra, C. R., & Ziegler, M. (2020). Adapting with microbial help: Microbiome flexibility facilitates rapid responses to environmental change. *Bioessays*, *42*(7), 2000004. https://doi.org/10.1002/bies.202000004
164. Doolittle, W. F., & Booth, A. (2017). It's the song, not the singer: An exploration of holobiosis and evolutionary theory. *Biology & Philosophy*, *32*(1), 5–24. https://doi.org/10.1007/s10539-016-9542-2
165. Wargo, J. A. (2020). Modulating gut microbes. *Science*, *369*(6509), 1302–1303. https://doi.org/10.1126/science.abc3965
166. Rautava, S., Kalliomaki, M., & Isolauri, E. (2005). New therapeutic strategy for combating the increasing burden of allergic disease: Probiotics-A Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota (NAMI) Research Group report. *Journal of Allergy and Clinical Immunology*, *116*(1), 31–37. https://doi.org/10.1016/j.jaci.2005.02.010
167. Zaneveld, J., Turnbaugh, P. J., Lozupone, C., Ley, R. E., Hamady, M., Gordon, J. I., & Knight, R. (2008). Host-bacterial coevolution and the search for new drug targets. *Current Opinion in Chemical Biology*, *12*(1), 109–114. https://doi.org/10.1016/j.cbpa.2008.01.015
168. Lynch, M. (2016). Mutation, eugenics, and the boundaries of science. *Genetics*, *204*(2), 825–827. https://doi.org/10.1534/genetics.116.194621
169. Lynch, M. (2016). Mutation and human exceptionalism: Our future genetic load. *Genetics*, *202*(3), 869–875. https://doi.org/10.1534/genetics.115.180471
170. Ding, J., Frantzeskos, A., & Orozco, G. (2020). Functional genomics in autoimmune diseases. *Human Molecular Genetics*, *29*(R1), R59–R65. https://doi.org/10.1093/hmg/ddaa097
171. Kadosh, E., Snir-Alkalay, I., Venkatachalam, A., May, S., Lasry, A., Elyada, E., Zinger, A., Shaham, M., Vaalani, G., Mernberger, M., Stiewe, T., Pikarsky, E., Oren, M., & Ben-Neriah, Y. (2020). The gut microbiome switches mutant p53 from tumour-suppressive to oncogenic. *Nature*, *586*, 133–138. https://doi.org/10.1038/s41586-020-2541-0
172. Greenspan, S. E., Migliorini, G. H., Lyra, M. L., Pontes, M. R., Carvalho, T., Ribeiro, L. P., Moura-Campos, D., Haddad, C. F. B., Toledo, L. F., Romero, G. Q., & Becker, C. G. (2020). Warming drives ecological community changes linked to host-associated microbiome dysbiosis. *Nature Climate Change*, *10*, 1057–1061. https://doi.org/10.1038/s41558-020-0899-5
173. Inkpen, S. A. (2019). Health, ecology and the microbiome. *ELife*, *8*, e47626. https://doi.org/10.7554/eLife.47626

How to cite this article: Catania, F., Baedke, J., Fábregas-Tejeda, A., Nieves Delgado, A., Vitali, V., & Nguyen Long, L. (2021). Global climate change, diet and the complex relationship between human host and microbiome: Towards an integrated picture. *BioEssays*, e2100049. https://doi.org/10.1002/bies.202100049