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PERSPECTIVE

Perspectives on Inequity and Health Disparities in Chile and Their Relationship to Microbial Ecology

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ABSTRACT Among countries in the Organisation for Economic Cooperation and Development (OECD), Chile stands out as having important inequalities in income distribution, dietary quality, access to urban green spaces, and health outcomes. People in lower socioeconomic groups consistently show higher rates of noncommunicable chronic diseases and are being hit the hardest by the COVID-19 pandemic. These chronic conditions are increasingly considered to be shaped, or affected by, the human gut microbiome. Moreover, inequity as an overarching concept might also be associated with microbial patterns and if so, this may represent a novel pathway through which to address health and other disparities. Focusing on the case of Chile, our goal is to contribute to a critical discussion and motivate researchers and policymakers to consider the role of the microbiome in social equity in future endeavors.

KEYWORDS health, microbiota, inequity, Chile, green space, lifestyle

Noncommunicable chronic diseases (NCDs) are a major contributor to the burden of disease worldwide (1). Despite their widespread prevalence, the distribution of these conditions is not equitable across countries and differs greatly within populations according to differences in socioeconomic status (SES) and other social determinants (2). A relative newcomer in the understanding of the mechanisms underlying NCD development is the gut microbiome, and differences in the prevalence of these diseases across communities appear to be influenced by it (3). The relationship between health and the human gut microbiome has recently received increasing attention (4). It is now widely acknowledged that several factors influence its composition, including delivery method at birth, breastfeeding, exposure to antibiotics during infancy, nutrition, and urbanization/exposure to green spaces, among others (5).

In this paper, we discuss to what extent inequity and the microbiome are linked as risk factors for health status, with a distinct focus on Chile. First, we review health and other inequities within the Chilean population. We then provide an overview of global human microbiome determinants. Finally, we explore potential pathways linking these inequities and the microbiome in the Chilean context.

INEQUITY IN CHILE

Among the Organisation for Economic Co-operation and Development (OECD), Chile is one of the most unequal countries (6). It is estimated that the richest 1% captures 17% of the total tax revenue, while the wealthiest 10% receives over 50% of all income (7). The origins of inequality in Chile can be traced back to European colonialism, the consequences of which are still prominent today (8). Notable disparities encompass culture, health care access, nutrition, air pollution, and access to green spaces, among others (9). Inequities within these dimensions may have an impact on Chileans' microbiomes and will now be reviewed.

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Inequality of green spaces. According to the World Health Organization (WHO), every city is recommended to provide a minimum of 9 m^2 of urban green space per capita (10, 11). Chile's Metropolitan region (where the capital Santiago is located) has an average of 3.2 m^2 of urban green space per capita, with a very unequal distribution (12). One study showed the poorest sectors' ratio ranged between 0.4 and 2.9 m^2/person, while higher-income areas' ratio was 6.7 to 18.8 m^2/person (13). Distance to green space from a given household is larger in poorer sectors and accessibility is worse (13). Additionally, low-income neighborhoods have much lower vegetation or green cover in their parks or public squares, compared with higher-income areas. Vegetation cover ranges from less than 27% in poorer districts to over 70% in the wealthiest (14). Plant species' richness yields greater soil microbial diversity, which has potential implications for human health and health equity (15). It follows that this disparity may have tangible health benefits for the rich, and detriments for the poor.

Health disparities. Chile has a high prevalence of various NCDs. The prevalence of obesity is 34.4% while 39.8% of the population is overweight (16), representing the second-highest excess weight prevalence within OECD countries (17). The prevalence of type 2 diabetes in 2017 was 12.3%, rising from 9.4% in 2010 (18). This places Chile as the sixth country with the highest diabetes rates among the OECD (19).

In the realm of mental health, depressive disorders are some of the most widespread diseases, showing a prevalence of 6,8%, according to the National Health Survey from 2017 (16). Data disaggregated by gender reveals a much higher prevalence of depression among Chilean women compared with Chilean men: 10.1% versus 2.1%, respectively. These diseases exist within a *social gradient* (20), where a lower income and overall SES correlate with a higher prevalence of NCDs, while the opposite is also true. Unsurprisingly, lifestyle-related risk factors for these chronic diseases, such as low levels of physical activity and poor dietary quality, are more widespread in Chileans of lower SES (21, 22).

Obesity, diabetes, other NCDs, and depression are to some extent mediated by the gut microbiome. The behavioral and environmental risk factors that catalyze the onset of these diseases have an impact on the gut microbiome (23). The next section will consider some of these microbiome determinants and then discuss potential links to health inequities in Chile.

MICROBIOME DETERMINANTS ACROSS THE LIFE-COURSE

First microbiome determinants. Childbirth delivery method is considered the first major microbiome determinant (24). While natural delivery allows the vertical maternal-newborn transmission of vaginal microbiota, caesarean delivery is characterized by colonization of skin microorganisms (24), which may have implications for asthma, allergies, and other inflammatory conditions (25). Breastfeeding is considered a protective factor for those conditions and represents the main microbiota covariate through the first year of life (26), regardless of delivery method. This might have important health implications in Chile, where breastfeeding rates at the sixth month of life are estimated at 44% (27, 28). Other microbiome determinants such as antibiotic use during childhood may contribute to conditions such as obesity and becoming overweight (29), but data on this relationship is scarce in Chile.

Nutrition and the gut microbiome. During adolescence, the microbiome is influenced by several physiological and environmental cues, which slowly change and develop into adulthood (30). In adulthood, an important determinant of the gut environment is diet (31). Eating patterns high in whole grains, fruits, and vegetables, such as the Mediterranean diet, have been associated with increased microbial diversity and stability (32). Conversely, western diets (i.e., high in ultraprocessed foods) or fad diets (e.g., ketogenic, paleolithic) are related to diminished microbial abundance and diversity (33). Diets lacking enough fiber content decrease the gut's mucus thickness and induce a "leaky gut" (34) and the expression of proinflammatory markers (35). Conversely, fiber intake favors "beneficial" bacteria growth, particularly those species specialized in short-chain fatty acid production such as butyrate, acetate, and propionate (36). Cross-sectional studies in Chile show that among preschool children, almost 50% of dietary calories come from ultraprocessed foods low in fiber (37). In adults, this amounts to almost 30% of total calorie intake (38, 39).

Urbanization and green space exposure. The built environment exerts an important influence on the human microbiome across the life-course, as both host and environmental microbiomes are interconnected and exchange microorganisms regularly (40). Urban sectors often have depleted microbial biodiversity (41–43), which is relevant because this influences the composition of the human gut, nasal, and skin microbiomes, and because a diverse gut microbiome has been identified as a health predictor (44). Furthermore, studies looking at the effects of the aerobiome (the collection of microorganisms in a given airspace) on murine models have shown that it affects their guts' microbial composition, short-chain fatty acid production, and has anxiolytic effects (45). Also, evidence shows vertical stratification of the vegetation in greenspaces influences the aerobiome composition, with potential implications for human health (46).

Over half of the global population lives in urban areas and over two-thirds are predicted to embrace urbanization by midcentury (https://ourworldindata.org/grapher/urban-and-rural-population-2050?country=~OWID_WRL). Chile is no exception, as 88.6% of its population lives in urban areas and this number is projected to continue rising (47). Urbanization disturbs soil properties and alters the diversity of its microbial communities (48). The loss of microbial diversity has potential consequences for urban dwellers' microbiomes and it has been called a "*major public health threat*" by researchers (49).

Despite the influence of these microbiome determinants, pharmaceuticals appear to be stronger drivers of the composition of the gut microbiome in adults. This has been the case in Western European and American cohorts (50, 51). Nevertheless, the role of lifestyle and environmental exposures should not be underestimated, as studies looking at the gut microbiome of hunter-gatherers' communities show important differences with urban controls (43). Interventions modifying the biodiversity of the built environment show that this has an impact on the hosts' skin and gut microbiomes (52).

Contrasting social realities are underpinned by different lifestyles and environmental exposures. Potential links between the microbiome and health and social inequities will now be explored.

IS THERE A RELATIONSHIP BETWEEN INEQUITY AND THE HUMAN MICROBIOME?

To date, most of the studies on the human microbiome have been conducted in European (53) or North American populations (54). Few studies look at the microbiomes of Latin Americans or specifically Chileans (55). This issue is likely worse for ethnic minorities in Chile and even more so among indigenous communities. Learning more about the microbiota of Chilean individuals and communities is key to better understanding the potential relationships between health, inequity, and local gut microbiomes.

Lower-income citizens live in areas lacking enough urban green space and with less diverse vegetation. Close contact with nature has been shown to reduce the risk of mental illnesses (e.g., depressive disorder) and it is also a protective factor against NCDs (e.g., hypertension, cardiovascular risk factors) (56, 57). This happens through various pathways, some of which involve interactions between host and environmental microbiomes (58, 59). Therefore, inequities in green space distribution and access are likely to promote a less biodiverse gut microbiome among the most disadvantaged, with potentially negative consequences for their health (58).

On the other hand, Chileans of low SES consume unhealthy diets low in fiber and high in processed foods (16), which are an established risk factor for several NCDs (60, 61). One of the underlying physiological mechanisms leading from unhealthy diets to chronic diseases is the microbiome, as a lack of dietary fiber and the intake of processed foods' ingredients have been shown to have a negative impact on the microbiomes of both animal and human models (62–64). These data and relationships raise a very important possibility; the *social gradient*, whereby lower-income populations in Chile have a higher prevalence of NCDs with a lower life expectancy (65), might also exist as an "enterotype gradient" of sorts, where multidimensional inequities may be reflected in distinct gut microbial communities' relative abundance. In fact, some evidence suggests lower SES is associated with reduced gut microbial alpha diversity (66), a phenomenon usually considered detrimental to health (67), and family SES can predict microbial beta diversity in the gut from an early age (68).

The available evidence cannot yet establish a conclusive causal relation between green space access, dietary inequities, NCDs prevalence, socioeconomic background, and the microbiome. Yet, the existing data are arguably sufficient to support the need to enhance opportunities for marginalized populations to protect their health through interventions that restore their microbiomes. Interventions targeting the gut microbiome could diminish health inequities and be part of—or complementary to—broader policy development. An increasing volume of research is suggesting that *biodiverse urban greenspaces* (BUGS) improve urban dweller's microbiomes with positive consequences for health (69–71). Or as the microbiome rewilding hypothesis purports, "restoring biodiverse habitats in urban green spaces can rewild the environmental microbiome to a state that enhances primary prevention of human disease" (72).

A study that manipulated the plant and microbial diversity of green spaces in a children's day care center, found that this had an impact on children's gut and skin microbiomes and enhanced immunoregulatory pathways (52). Another study showed that the biodiversity of the schoolyard environment influences recovery periods of human skin microbiota after its disturbance in children (73). Considering that vegetation cover in Chilean schools is profoundly unequal across the socioeconomic spectrum, with wealthier private schools having much more green cover than their poorer public counterparts (74), there is a great opportunity in Chile to replicate these interventions and apply them to the school environment. This has the potential to diminish health inequities from childhood, by increasing children's exposure to environmental microbial diversity and providing more recreational spaces for physical activity and social interaction.

Beyond the school environment, considering how unequal urbanization attributes are in Chile, there is an important occasion for public policy to promote healthier cities. The use of targeted *nature-based health interventions/prescriptions*, which aim to expose individuals to somewhat structured nature-based experiences to promote health and wellbeing (75), could enhance exposure to environmental microbes and ascertain beneficial microbial communities within the human microbiota (76). This has the potential to lower the risk of NCDs and their health consequences (77).

When examining the relationships between social inequities, microbial ecology, and health, one can go a step further and consider inequity and the microbiome as enhancers or mediators of a *syndemic*; the complex aggregation of apparently independent diseases embedded in an unequal societal context, exacerbating the adverse effects of each condition (78). Each health condition is exacerbated by socioeconomic disparities, not as simple comorbidities. Approaching the problem from the perspective of a syndemic could aid in the understanding and management of the risk factors promoting the trends previously described, and novel strategies involving microbial rewilding strategies may play a role in this. Similarly, theoretical approaches that *do justice* to such complexity are needed (79–81). Novel, integrative approaches are of utmost importance for the >10% of the Chilean population living below the poverty line and the poorest billion people on the planet (82).

FUTURE DIRECTIONS

At the time of this writing, Chile is in the middle of a crucial process regarding social equity. A democratically elected constitutional convention is designing a new constitution for the country. This could be the perfect opportunity for policy-makers, politicians, health professionals, environmental health experts, and academics, to collaborate across disciplines and address inequity from a perspective that goes beyond direct economic considerations. Increasing access and availability of urban recreational grounds may not be enough, and perhaps more *biodiverse urban green space* is needed. A potential first step toward the latter is granting constitutional protection to biodiversity (including microbial biodiversity), as the president of the Chilean Society of Microbiology recently suggested (https://somich.cl/la-diversidad-de-los-microorganismos-a-la-constitucion/).

Conversely, educating the population on healthy food choices is an underserved endeavor, and policies regulating the publicity of processed foods should be strengthened.

Mental health and NCDs must be addressed in an integrative way; future research should investigate the possibility of an "enterotype gradient" and develop targeted interventions to improve key microbial functions in the gut. Dietary interventions that promote the intake of more fiber have shown that the gut microbiome can quickly change its composition (83, 84).

Furthermore, promoting low-cost, population-based public health interventions encompassing transdisciplinary perspectives can be more cost-effective and successful in the long-term, than spending most budget, time, and effort on mitigating proximal or immediate causes of disease. Addressing inequity implies directing most of our focus on its causes rather than its symptoms; transdisciplinary efforts that integrate microbial ecology, lifestyles, psychology, and brain and medical sciences, may have something important to say in this endeavor (85).

REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396:1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9.
2. Dugravot A, Fayosse A, Dumurgier J, Bouillon K, Ben Rayana T, Schnitzler A, Kivimaki M, Sabia S, Singh-Manoux A. 2020. Social inequalities in multimorbidity, frailty, disability, and transitions to mortality: a 24-year follow-up of the Whitehall II cohort study. Lancet Public Health 5:42–50.
3. Hills RD, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR. 2019. Gut microbiome: profound implications for diet and disease. Nutrients 11:1613–1640. https://doi.org/10.3390/nu11071613.
4. Prados-Bo A, Casino G. 2021. Microbiome research in general and business newspapers: how many microbiome articles are published and which study designs make the news the most? PLoS One 16:e0249835–14. https://doi.org/10.1371/journal.pone.0249835.
5. Hasan N, Yang H. 2019. Factors affecting the composition of the gut microbiota, and its modulation. PeerJ 7:e7502–31. https://doi.org/10.7717/peerj.7502.
6. OECD. 2021. Economic Survey of Chile. Available at https://www.oecd.org/economy/surveys/Chile-2021-OECD-economic-survey-overview.docx.pdf.
7. Flores I, Sanhueza C, Atria J, Mayer R. 2020. Top incomes in Chile: a historical perspective on income inequality, 1964–2017. Rev Income Wealth 66:850–874. https://doi.org/10.1111/roiw.12441.
8. Nahuelpan Moreno HJ, Antimil Caniupán JA. 2019. Republican colonialism, violence and Mapuche racial subordination in Chile during the twentieth century. HiSTOReLo 11:211–248.
9. Programa de las Naciones Unidas para el desarrollo. 2017. Desiguales: orígenes, cambios y desafíos de la brecha social en Chile. Ograma Impresores, Santiago de Chile.
10. World Health Organization. 2010. Urban planning, environment and health: from evidence to policy action - meeting report. EuroWhoInt.
11. Morar T, Radoslav R, Spiridon LC, Păcurar L. 2014. Assessing pedestrian accessibility to green space using GIS. Transylvanian Rev Adm Sci:116–139.
12. Nilo C. 2003. Plan Verde: un instrumento para la gestión y fomento de áreas verdes en el gran Santiago. Urbano 6:10–15.
13. Reyes PS, Figueroa AI. 2010. Distribución, superficie y accesibilidad de las áreas verdes en Santiago de Chile. Eure 36:89–110.
14. Truffello R. 2019. Observatorio de ciudades UC: Desigualdades en el porcentaje de biomasa en comunas de la Región Metropolitana. https://www.pauta.cl/calidad-de-vida/estadisticas-parques-espacios-verdes-ciudades-regiones-de-chile
15. Baruch Z, Liddicoat C, Cando-Dumancela C, Laws M, Morelli H, Weinstein P, Young JM, Breed MF. 2021. Increased plant species richness associates with greater soil bacterial diversity in urban green spaces. Environmental Res Elsevier BV 196:110425. https://doi.org/10.1016/j.envres.2020.110425.
16. Ministerio de Salud. 2017. Encuesta Nacional de Salud 2016–2017 Primeros resultados. Departamento Epidemiologia, División Planificación Sanitaria Subsecretaría Salud Pública 61, Santiago de Chile.
17. OECD. 2017. Obesity update 2017. Diabetologe 13:331–341. https://doi.org/10.1007/s11428-017-0241-7.
18. Sapunar J. 2016. Chilean epidemiology in diabetes mellitus. Rev Clínica Las Condes 27:146–151. https://doi.org/10.1016/j.rmclc.2016.04.003.
19. OECD. 2017. Health at a glance 2017. OECD.
20. Marmot M, Bell R. 2016. Social inequalities in health: a proper concern of epidemiology. Ann Epidemiol 26:238–240. https://doi.org/10.1016/j.annepidem.2016.02.003.
21. MINSAL. Ministerio de Salud del Gobierno de Chile. 2015. Encuesta nacional de consumo alimentario antecedentes. Encuesta Consum 1:1–33.
22. Garrido-Méndez Á, Matus-Castillo C, Poblete-Valderrama F, Flores-Rivera C, Petermann-Rocha F, Rodríguez-Rodríguez F, Vásquez-Gómez J, Díaz-Martínez X, Beltrán AR, Celis-Morales C. 2020. Nivel educativo y su asociación con niveles de actividad física en Chile. Rev méd Chile 148:295–303.
23. Ahn J, Hayes RB. 2021. Environmental influences on the human microbiome and implications for noncommunicable disease. Annu Rev Public Health Annu Rev 42:277–292. https://doi.org/10.1146/annurev-publhealth-012420-105020.
24. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 107:11971–11975. https://doi.org/10.1073/pnas.1002601107.
25. Salam MT, Margolis HG, McConnell R, McGregor JA, Avol EL, Gilliland FD. 2006. Mode of delivery is associated with asthma and allergy occurrences in children. Ann Epidemiol 16:341–346. https://doi.org/10.1016/j.annepidem.2005.06.054.
26. Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, Ross MC, Lloyd RE, Doddapaneni H, Metcalf GA, Muzny D, Gibbs RA, Vatanen T, Huttenhower C, Xavier RJ, Rewers M, Hagopian W, Toppari J, Ziegler A-G, She J-X, Akolkar B, Lernmark A, Hyoty H, Vehik K, Krischer JP, Petrosino JF. 2018. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature 562:583–588. https://doi.org/10.1038/s41586-018-0617-x.
27. Ministerio de Salud. 2010. Manual de Lactancia Materna. Subsecretaría de Salud Pública, Departamento de Asesoría Jurídica, Santiago de Chile.
28. Ministerio de Salud. 2014. Vigilancia del estado nutricional de la población bajo control y de la lactancia materna en el sistema público de salud de Chile. Subsecretaría de Salud Pública, División Políticas Públicas Saludables y Promoción, Santiago de Chile.
29. Saari A, Virta LJ, Sankilampi U, Dunkel L, Saxen H. 2015. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. Pediatrics 135:617–626. https://doi.org/10.1542/peds.2014-3407.
30. McVey Neufeld K-A, Luczynski P, Dinan TG, Cryan JF. 2016. Reframing the teenage wasteland: adolescent microbiota-gut-brain axis. Can J Psychiatry 61:214–221. https://doi.org/10.1177/0706743716635536.
31. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen Y-Y, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. 2011. Linking long-term dietary patterns with gut microbial enterotypes. Science 334:105–108. https://doi.org/10.1126/science.1208344.
32. Merra G, Noce A, Marrone G, Cintoni M, Tarsitano MG, Capacci A, De Lorenzo A. 2020. Influence of mediterranean diet on human gut microbiota. Nutrients 13:7. https://doi.org/10.3390/nu13010007.
33. Rinninella E, Cintoni M, Raoul P, Lopetuso LR, Scaldaferri F, Pulcini G, Abele G, Miggiano D, Gasbarrini A, Mele MC. 2019. Food components and dietary habits: keys for a healthy gut microbiota composition. Nutrients 11:2393–2323. https://doi.org/10.3390/nu11102393.
34. Usuda H, Okamoto T, Wada K. 2021. Leaky gut: effect of dietary fiber and fats on microbiome and intestinal barrier. Int J Mol Sci 22:7613. https://doi.org/10.3390/ijms22147613.
35. Earle KA, Billings G, Sigal M, Lichtman JS, Gunnar C, Elias JE, Amieva MR, Casey K, Justin L. 2015. Quantitative imaging of gut microbiota spatial organization. Cell Host Microbe 18:478–488. https://doi.org/10.1016/j.chom.2015.09.002.

36. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. 2014. Diet rapidly alters the human gut microbiota. Nature 505:559–563. https://doi.org/10.1038/nature12820.
37. Araya C, Corvalán C, Cediel G, Taillie LS, Reyes M. 2021. Ultra-processed food consumption among Chilean preschoolers is associated with diets promoting non-communicable diseases. Front Nutr 8:601526. https://doi.org/10.3389/fnut.2021.601526.
38. Cediel G, Reyes M, Corvalán C, Levy RB, Uauy R, Monteiro CA. 2021. Ultra-processed foods drive to unhealthy diets: evidence from Chile. Public Health Nutr 24:1698–1707. https://doi.org/10.1017/S1368980019004737.
39. Pinto V, Landaeta-Díaz L, Castillo O, Villarroel L, Rigotti A, Echeverría G, ELANS Study Group. 2019. Assessment of diet quality in Chilean urban population through the Alternate Healthy Eating Index 2010: a cross-sectional study. Nutrients 11:891. https://doi.org/10.3390/nu11040891.
40. Schmeller DS, Courchamp F, Killeen G. 2020. Biodiversity loss, emerging pathogens and human health risks. Biodivers Conserv 29:3095–3102. https://doi.org/10.1007/s10531-020-02021-6.
41. Singh BK, Quince C, Macdonald CA, Khachane A, Thomas N, Al-Soud WA, Sørensen SJ, He Z, White D, Sinclair A, Crooks B, Zhou J, Campbell CD. 2014. Loss of microbial diversity in soils is coincident with reductions in some specialized functions. Environ Microbiol 16:2408–2420. https://doi.org/10.1111/1462-2920.12353.
42. Aronson MFJ, La Sorte FA, Nilon CH, Katti M, Goddard MA, Lepczyk CA, Warren PS, Williams NSG, Cilliers S, Clarkson B, Dobbs C, Dolan R, Hedblom M, Klotz S, Kooijmans JL, Kühn I, Macgregor-Fors I, Mcdonnell M, Mörtberg U, Pyšek P, Siebert S, Sushinsky J, Werner P, Winter M. 2014. A global analysis of the impacts of urbanization on bird and plant diversity reveals key anthropogenic drivers. Proc R Soc Lond B Biol Sci 281.
43. Schnorr SL, 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 AG, Crittenden AN. 2014. Gut microbiome of the Hadza hunter-gatherers. Nat Commun 5:1–12. https://doi.org/10.1038/ncomms4654.
44. World Health Organization, Secretariat of the Convention on Biological Diversity. 2015. Connecting global priorities: biodiversity and human health. WHO Press.
45. Liddicoat C, Sydnor H, Cando-Dumancela C, Dresken R, Liu J, Gellie NJC, Mills JG, Young JM, Weyrich LS, Hutchinson MR, Weinstein P, Breed MF. 2020. Naturally-diverse airborne environmental microbial exposures modulate the gut microbiome and may provide anxiolytic benefits in mice. Sci Total Environ 701:134684. https://doi.org/10.1016/j.scitotenv.2019.134684.
46. Robinson JM, Cando-Dumancela C, Antwis RE, Cameron R, Liddicoat C, Poudel R, Weinstein P, Breed MF. 2021. Exposure to airborne bacteria depends upon vertical stratification and vegetation complexity. Sci Rep 11:9516. https://doi.org/10.1038/s41598-021-89065-y.
47. Instituto Nacional de Estadísticas. 2019. Estimaciones y proyecciones de la población de Chile 2002-2035 totales regionales, población urbana y rural. Síntesis de resultados, Santiago de Chile.
48. Yan B, Li J, Xiao N, Qi Y, Fu G, Liu G, Qiao M. 2016. Urban-development-induced changes in the diversity and composition of the soil bacterial community in Beijing. Sci Rep 6:38811. https://doi.org/10.1038/srep38811.
49. Tasnim N, Abulizi N, Pither J, Hart MM, Gibson DL. 2017. Linking the gut microbial ecosystem with the environment: does gut health depend on where we live? Front Microbiol 8:1–8.
50. Falony G, Joossens M, Vieira-Silva S, Wang J, Darzi Y, Faust K, Kurilshikov A, Bonder MJ, Valles-Colomer M, Vandeputte D, Tito RY, Chaffron S, Rymenans L, Verspecht C, De Sutter L, Lima-Mendez G, D'hoe K, Jonckheere K, Homola D, Garcia R, Tigchelaar EF, Eeckhaudt L, Fu J, Henckaerts L, Zhernakova A, Wijmenga C, Raes J. 2016. Population-level analysis of gut microbiome variation. Science 352:560–564. https://doi.org/10.1126/science.aad3503.
51. Manor O, Dai CL, Kornilov SA, Smith B, Price ND, Lovejoy JC, Gibbons SM, Magis AT. 2020. Health and disease markers correlate with gut microbiome composition across thousands of people. Nat Commun 11:1–12. https://doi.org/10.1038/s41467-020-18871-1.
52. Roslund MI, Puhakka R, Grönroos M, Nurminen N, Oikarinen S, Gazali AM, Cinek O, Kramná L, Siter N, Vari HK, Soininen L, Parajuli A, Rajaniemi J, Kinnunen T, Laitinen OH, Hyöty H, Sinkkonen A, ADELE Research Group. 2020. Biodiversity intervention enhances immune regulation and health-associated commensal microbiota among daycare children. Sci Adv 6:eaba2578. https://doi.org/10.1126/sciadv.aba2578.
53. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, 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. Nat Microbiol 4:623–632. https://doi.org/10.1038/s41564-018-0337-x.
54. McDonald D, Hyde E, Debelius JW, Morton JT, Gonzalez A, Ackermann G, Aksenov AA, Behsaz B, Brennan C, Chen Y, DeRight Goldasich L, Dorrestein PC, Dunn RR, Fahimipour AK, Gaffney J, Gilbert JA, Gogul G, Green JL, Hugenholtz P, Humphrey G, Huttenhower C, Jackson MA, Janssen S, Jeste DV, Jiang L, Kelley ST, Knights D, Kosciolek T, Ladau J, Leach J, Marotz C, Meleshko D, Melnik AV, Metcalf JL, Mohimani H, Montassier E, Navas-Molina J, Nguyen TT, Peddada S, Pevzner P, Pollard KS, Rahnavard G, Robbins-Pianka A, Sangwan N, Shorenstein J, Smarr L, Song SJ, Spector T, Swafford AD, Thackray VG, The American Gut Consortium, et al. 2018. American gut: an open platform for citizen science microbiome research. mSystems 3:e00031-18. https://doi.org/10.1128/mSystems.00031-18.
55. Fujio-Vejar S, Vasquez Y, Morales P, Magne F, Vera-Wolf P, Ugalde JA, Navarrete P, Gotteland M. 2017. The gut microbiota of healthy Chilean subjects reveals a high abundance of the phylum Verrucomicrobia. Front Microbiol 8:1221. https://doi.org/10.3389/fmicb.2017.01221.
56. Dadvand P, Nieuwenhuijsen MJ, Esnaola M, Forns J, Basagaña X, Alvarez-Pedrerol M, Rivas I, López-Vicente M, De Pascual MC, Su J, Jerrett M, Querol X, Sunyer J. 2015. Green spaces and cognitive development in primary schoolchildren. Proc Natl Acad Sci U S A 112:7937–7942. https://doi.org/10.1073/pnas.1503402112.
57. Jimenez MP, DeVille NV, Elliott EG, Schiff JE, Wilt GE, Hart JE, James P. 2021. Associations between nature exposure and health: a review of the evidence. IJERPH 18:4790. https://doi.org/10.3390/ijerph18094790.
58. Mills JG, Brookes JD, Gellie NJC, Liddicoat C, Lowe AJ, Sydnor HR, Thomas T, Weinstein P, Weyrich LS, Breed MF. 2019. Relating urban biodiversity to human health with the "Holobiont" concept. Front Microbiol 10:1–8.
59. Robinson JM, Breed MF. 2020. The lovebug effect: is the human biophilic drive influenced by interactions between the host, the environment, and the microbiome? Sci Total Environ 720:137626. https://doi.org/10.1016/j.scitotenv.2020.137626.
60. Elizabeth L, Machado P, Zinöcker M, Baker P, Lawrence M. 2020. Ultra-processed foods and health outcomes: a narrative review. Nutrients 12:1955. https://doi.org/10.3390/nu12071955.
61. Barber TM, Kabisch S, Pfeiffer AFH, Weickert MO. 2020. The health benefits of dietary fibre. Nutrients 12:3209. https://doi.org/10.3390/nu12103209.
62. Gerasimidis K, Bryden K, Chen X, Papachristou E, Verney A, Roig M, Hansen R, Nichols B, Papadopoulou R, Parrett A. 2020. The impact of food additives, artificial sweeteners and domestic hygiene products on the human gut microbiome and its fibre fermentation capacity. Eur J Nutr 59:3213–3230. https://doi.org/10.1007/s00394-019-02161-8.
63. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, Weinberger A, Kuperman Y, Harmelin A, Kolodkin-Gal I, Shapiro H, Halpern Z, Segal E, Elinav E. 2014. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 514:181–186. https://doi.org/10.1038/nature13793.
64. Cronin P, Joyce SA, O'Toole PW, O'Connor EM. 2021. Dietary fibre modulates the gut microbiota. Nutrients 13:1655. https://doi.org/10.3390/nu13051655.
65. Fuentes-García A, Sánchez H, Lera L, Cea X, Albala C. 2013. Desigualdades socioeconómicas en el proceso de discapacidad en una cohorte de adultos mayores de Santiago de Chile. Gaceta Sanitaria Elsevier BV 27:226–232. https://doi.org/10.1016/j.gaceta.2012.11.005.
66. Miller GE, Engen PA, Gillevet PM, Shaikh M, Sikaroodi M, Forsyth CB, Mutlu E, Keshavarzian A. 2016. Lower neighborhood socioeconomic status associated with reduced diversity of the colonic microbiota in healthy adults. PLoS One 11:e0148952–17. https://doi.org/10.1371/journal.pone.0148952.
67. Pickard JM, Zeng MY, Caruso R, Núñez G. 2017. Gut microbiota: role in pathogen colonization, immune responses, and inflammatory disease. Immunol Rev 279:70–89. https://doi.org/10.1111/imr.12567.
68. Lewis CR, Bonham KS, McCann SH, Volpe AR, D'Sa V, Naymik M, De Both MD, Huentelman MJ, Lemery-Chalfant K, Highlander SK, Deoni SCL, Klepac-Ceraj V. 2021. Family SES is associated with the gut microbiome in infants and children. Microorganisms MDPI AG 9:1608. https://doi.org/10.3390/microorganisms9081608.
69. Flies EJ, Skelly C, Negi SS, Prabhakaran P, Liu Q, Liu K, Goldizen FC, Lease C, Weinstein P. 2017. Biodiverse green spaces: a prescription for global urban health. Front Ecol Environ 15:510–516. https://doi.org/10.1002/fee.1630.
70. Mills JG, Brookes JD, Gellie NJC, Liddicoat C, Lowe AJ, Sydnor HR, Thomas T, Weinstein P, Weyrich LS, Breed MF. 2019. Relating urban biodiversity to human health with the 'holobiont' concept. Front Microbiol 10:550. https://doi.org/10.3389/fmicb.2019.00550.
71. Williams CR, Burnell SM, Rogers M, Flies EJ, Baldock KL. 2021. Nature-based citizen science as a mechanism to improve human health in urban areas. IJERPH 19:68. https://doi.org/10.3390/ijerph19010068.

72. Mills JG, Weinstein P, Gellie NJC, Weyrich LS, Lowe AJ, Breed MF. 2017. Urban habitat restoration provides a human health benefit through microbiome rewilding: the microbiome rewilding hypothesis. Restor Ecol 25:866–872. https://doi.org/10.1111/rec.12610.
73. Mills JG, Selway CA, Thomas T, Weyrich LS, Lowe AJ. 2022. Schoolyard biodiversity determines short-term recovery of disturbed skin microbiota in children. Microb Ecol https://doi.org/10.1007/s00248-022-02052-2.
74. Fernández IC, Pérez-Silva R, Villalobos-Araya E. 2022. Vegetation cover within and around schools in Santiago de Chile: are schools helping to mitigate urban vegetation inequalities? Urban Forestry & Urban Greening 70:127520. https://doi.org/10.1016/j.ufug.2022.127520.
75. Shanahan DF, Astell-Burt T, Barber EA, Brymer E, Cox DTC, Dean J, Depledge M, Fuller RA, Hartig T, Irvine KN, Jones A, Kikillus H, Lovell R, Mitchell R, Niemelä J, Nieuwenhuijsen M, Pretty J, Townsend M, van Heezik Y, Warber S, Gaston KJ. 2019. Nature-based interventions for improving health and wellbeing: the purpose, the people and the outcomes. Sports (Basel) 7:141. https://doi.org/10.3390/sports7060141.
76. Tischer C, Kirjavainen P, Matterne U, Tempes J, Willeke K, Keil T, Apfelbacher C, Täubel M. 2022. Interplay between natural environment, human microbiota and immune system: a scoping review of interventions and future perspectives towards allergy prevention. Sci Total Environ 821:153422. https://doi.org/10.1016/j.scitotenv.2022.153422.
77. Amato KR, Arrieta MC, Azad MB, Bailey MT, Broussard JL, Bruggeling CE, Claud EC, Costello EK, Davenport ER, Dutilh BE, Swain Ewald HA, Ewald P, Hanlon EC, Julion W, Keshavarzian A, Maurice CF, Miller GE, Preidis GA, Segurel L, Singer B, Subramanian S, Zhao L, Kuzawa CW. 2021. The human gut microbiome and health inequities. Proc Natl Acad Sci U S A 118:1–10.
78. Singer M, Bulled N, Ostrach B, Mendenhall E. 2017. Syndemics and the biosocial conception of health. Lancet 389:941–950. https://doi.org/10.1016/S0140-6736(17)30003-X.
79. Mackenzie JS, Jeggo M. 2019. The One Health approach—why is it so important? TropicalMed 4:88. https://doi.org/10.3390/tropicalmed4020088.
80. Palacios-García I, Parada FJ. 2021. The holobiont mind: a bridge between 4E cognition and the microbiome. Adaptive Behavior. https://doi.org/10.1177/10597123211053071.
81. Palacios-García I, Mhuireach GA, Grasso-Cladera A, Cryan JF, Parada FJ. 2022. The 4E approach to the human microbiome: nested interactions between the gut-brain/body system within natural and built environments. BioEssays 44:2100249. https://doi.org/10.1002/bies.202100249.
82. Bukhman G, Mocumbi AO, Atun R, Becker AE, Bhutta Z, Binagwaho A, Clinton C, Coates MM, Dain K, Ezzati M, Gottlieb G, Gupta I, Gupta N, Hyder AA, Jain Y, Kruk ME, Makani J, Marx A, Miranda JJ, Norheim OF, Nugent R, Roy N, Stefan C, Wallis L, Mayosi B, Adjaye-Gbewonyo K, Adler A, Amegashie F, Amuyunzu-Nyamongo MK, Arwal SH, Bassoff N, Beste JA, Boudreaux C, Byass P, Cadet JR, Dagnaw WW, Eagan AW, Feigl A, Gathecha G, Haakenstad A, Haileamlak AM, Johansson KA, Kamanda M, Karmacharya B, Kasomekera N, Kintu A, Koirala B, Kwan GF, Larco NC, Maongezi S, Lancet NCDI Poverty Commission Study Group, et al. 2020. The Lancet NCDI Poverty Commission: bridging a gap in universal health coverage for the poorest billion. Lancet 396:991–1044. https://doi.org/10.1016/S0140-6736(20)31907-3.
83. Oliver A, Chase AB, Weihe C, Orchanian SB, Riedel SF, Hendrickson CL, Lay M, Sewall JM, Martiny JBH, Whiteson K. 2021. High-fiber, whole-food dietary intervention alters the human gut microbiome but not fecal short-chain fatty acids. mSystems 6. https://doi.org/10.1128/msystems.00115-21.
84. Adithya KK, Rajeev R, Selvin J, Seghal Kiran G. 2021. Dietary influence on the dynamics of the human gut microbiome: prospective implications in interventional therapies. ACS Food Sci Tech 1:717–736. https://doi.org/10.1021/acsfoodscitech.0c00075.
85. Ishaq SL, Parada FJ, Wolf PG, Bonilla CY, Carney MA, Benezra A, Wissel E, Friedman M, DeAngelis KM, Robinson JM, Fahimipour AK, Manus MB, Grieneisen L, Dietz LG, Pathak A, Chauhan A, Kuthyar S, Stewart JD, Dasari MR, Nonnamaker E, Choudoir M, Horve PF, Zimmerman NB, Kozik AJ, Darling KW, Romero-Olivares AL, Hariharan J, Farmer N, Maki KA, Collier JL, O'Doherty KC, Letourneau J, Kline J, Moses PL, Morar N. 2021. Introducing the microbes and social equity working group: considering the microbial components of social, environmental, and health justice. mSystems 6. https://doi.org/10.1128/mSystems.00471-21.