OPINION

Urbanization and the gut microbiota in health and inflammatory bowel disease

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Abstract | In the 21st century, urbanization represents a major demographic shift in developed and developing countries. Rapid urbanization in the developing world has been associated with an increasing incidence of several autoimmune diseases, including IBD. Patients with IBD exhibit a decrease in the diversity and richness of the gut microbiota, while urbanization attenuates the gut microbial diversity and might have a role in the pathogenesis of IBD. Environmental exposures during urbanization, including Westernization of diet, increased antibiotic use, pollution, improved hygiene status and early-life microbial exposure, have been shown to affect the gut microbiota. The disparate patterns of the gut microbiota composition in rural and urban areas offer an opportunity to understand the contribution of a 'rural microbiome' in potentially protecting against the development of IBD. This Perspective discusses the effect of urbanization and its surrogates on the gut microbiome (bacteriome, virome, mycobiome and helminths) in both human health and IBD and how such changes might be associated with the development of IBD.

There is an emerging consensus that urbanization is influencing human health despite its economic importance and contribution to development. The rapid urbanization experienced in the developing world has been associated with an increasing incidence of many forms of diseases, including IBD, obesity and diabetes mellitus[1–3]. Urbanization, a term used to describe the process through which a society transitions from a rural to an urban way of life and encompassing the gradual increase of the proportion of people living in urban areas, is one of the major demographic characteristics of the 21st century[4]. It is a multidimensional process that manifests as rapidly changing population characteristics and land cover[5]. Research on modern urban living and the way that it affects human health and autoimmune diseases has been well documented, but our understanding of the role of the gut microbiota in relation to factors associated with urbanization is still in its infancy. The effects of rapid urbanization are likely to be reflected in the human gut microbiome, and alterations in the gut microbiome have been associated with inflammatory and autoimmune diseases[6]. The role of the gut bacterial microbiome in human health and diseases has been extensively discussed elsewhere[7,8]. In this Perspective, we focus primarily on the effect of urbanization on the microbiome in both human health and IBD. We also discuss the effects of various markers or surrogate markers of urbanization, including changes in diet, antibiotic use and pollution, on the gut microbiome and how these factors influence the development of IBD. In addition to the gut bacterial microbiome, the virome, mycobiome and helminths are also discussed.

Urbanization and IBD epidemiology

IBD is a chronic inflammatory disorder of the gastrointestinal tract involving dysregulated immune activation towards the gut microbiota in genetically susceptible individuals[9]. Crohn's disease and ulcerative colitis are the two major forms of IBD, which lead to substantial morbidity and health-care costs[10,11]. The incidence of IBD has increased since the middle of the 20th century; >3 million individuals currently have IBD in Europe, and 5 million individuals have IBD globally[12–14]. At the turn of the 21st century, the incidence of IBD plateaued in some developed nations with a prevalence of up to 0.5% of the general population, although it has continued to rise in developing countries as well as in some developed countries[15–18]. Over the past few decades, IBD has emerged as a growing problem in low incidence areas, particularly in newly industrialized regions, including Asia, the Middle East and South America[19–23]. The emergence of IBD in these countries, many of which are undergoing rapid urbanization, resembles patterns that were observed in the Western world during the early 20th century, with the increasing prevalence of ulcerative colitis preceding that of Crohn's disease in urban areas[16,24]. Asia is one of the most rapidly urbanizing continents in the world[25]. The rapidly increasing incidence of IBD in newly industrialized Asian countries has been reported by the Asia–Pacific Crohn's and Colitis Epidemiology Study (ACCESS), which compared the incidence of IBD in Australia with that of China, Hong Kong, Sri Lanka, Indonesia, Singapore, Macau, Thailand and Malaysia[19]. These data showed that the highest incidence of IBD in Asia lies within highly urbanized regions, such as Hong Kong, Macau and Guangzhou, whereas regions with less industrialization and more rural inhabitants exhibited lower disease incidences[19].

A meta-analysis of 40 studies investigating the relationship between urban environment and IBD found that the pooled incidence rate ratios (IRRs) for urban compared with rural environments were 1.17 (95% CI 1.03–1.32) and 1.42 (95% CI 1.26–1.60) for ulcerative colitis and Crohn's disease, respectively[26], suggesting a link between urbanization and the development of IBD. The relative risk in the urban areas is about 1.3 as compared with the countryside[26].

In a Canadian population-based cohort study[27], the incidence of IBD was 7.3 per 100,000 person-years in immigrants and 23.9 per 100,000 person-years in non-immigrants (IRR 0.34, 95% CI 0.26–0.44). Children of immigrants from the Middle East, North Africa, South Asia, sub-Saharan

Africa and North America or Western Europe had a similar risk of IBD as children of non-immigrants, and a younger age at arrival to Canada increased the risk of IBD in immigrants. Furthermore, Canadian-born children of immigrants from some regions assumed the high Canadian incidence of IBD, supporting an important role of Western lifestyle in IBD development[27].

The adoption of Western lifestyle and diet, exposure to increased levels of pollution and improvement in hygiene practice and health care have accompanied the transition from a rural to an urban environment. Urbanization alone might not explain all the epidemiological changes of IBD in developed countries; for example, the rapid increase in IBD incidence in cities in Japan (for example, Tokyo), which is considered a highly urbanized area, and the rising incidence of Crohn's disease that has been described in several European countries, including France[18,28,29]. Nonetheless, exposure to a multitude of environmental factors, such as diet, antibiotics and pollution in early life might be associated with the loss of specific bacterial species of our ancestral microbiota and hence might contribute to the rising incidence of IBD[30].

IBD is known to manifest in genetically susceptible individuals with an exaggerated immune response to intestinal microorganisms in the presence of exposure to environmental triggers[31] and has traditionally been regarded as a disease of European descent. Although >200 genetic loci have been documented to confer a risk of IBD in white indiviudals[32–34], these genetic variants appeared to be different in Asian individuals with IBD[35,36]. Many of the well-established risk loci described in white individuals, including *NOD2* and *ATG16L*, have not been replicated in Asians with Crohn's disease[36]. As genetic factors, unlike the environment, cannot shift in the span of a single generation, genes alone cannot account for the rise in IBD incidence seen in non-Western countries at the turn of the 21st century. This rapid increase in the incidence in Asia therefore supports the view that IBD results from complex interactions between the host and the environment, an interplay modulated by the human gut microbiota[37,38]. Accumulating evidence suggests that the gut microbiota is a key factor in modulating the host immune system[39], influencing a predisposition to autoimmune diseases, including IBD[40].

Immigration studies have demonstrated that migrants emigrating from developing to developed countries that adopt a Western lifestyle have an increased risk of IBD[41,42]. Children are particularly affected by risk factors from the new environment, whereas their parents maintain their original risk, suggesting the importance of environmental influence in early childhood[42]. The effects of migration on the gut microbiome are largely unknown, but the changes in gut microorganisms in immigrant populations and how that might intersect with high rates of obesity, diabetes and other chronic diseases are being investigated.

The gut bacterial microbiome

Compositional differences. To date, there is no direct evidence about how urbanization affects the configuration of the gut microbiome in IBD. In addition, no studies have investigated the relationship between rural versus urban microbiomes and IBD development within populations of the same genetic background. Most of the data assessing the role of urbanization on the gut microbiome have been derived from comparative studies of the microbiome in rural and urban areas in healthy individuals. These studies have reported that populations residing in non-Western and/or rural areas have a higher bacterial diversity when compared with populations in America and Europe[43–46]. The faecal microbiota of children from a rural African village of Burkina Faso, who mostly consume a diet high in fibre, is similar to that of the microbiome of early human settlement at the time of the birth of agriculture[43]. Children from Burkina Faso exhibit a significant ($P < 0.001$) enrichment of Bacteroidetes and a depletion of Firmicutes compared with children from the urban area of Florence, Italy, with a unique abundance of bacteria from the genera *Prevotella* and *Xylanibacter*, which are known to contain a set of bacterial genes for cellulose and xylan hydrolysis. These bacteria were completely lacking in the 15 European children studied[43]. Similar findings have been observed in children and adults in Malawi, Amazonian American Indians[45] and adult Hadza hunter–gatherers in Tanzania[44]. These studies have demonstrated that urbanization is associated with an increased proportion of *Bacteroides*, *Alistipes* (Bacteroidetes), *Blautia*, *Faecalibacterium*, *Ruminococcus* (Firmicutes), *Bifidobacterium* (Actinobacteria) and *Bilophila* (Proteobacteria), whereas *Prevotella* (Bacteroidetes) is increased in the gut microbiota of individuals residing in non-industrialized societies[43–45].

There is a paucity of studies comparing the rural and urban microbiome within a population of homogeneous ethnicity. In a study comparing the faecal microbiota composition of African descendants living in rural, semi-urban areas with those living in urban areas, substantial differences were identified, with *Prevotella* predominating in semi-urban individuals and *Bacteroides* predominating in urban African Americans[47]. These findings suggest that the gut microbiota composition differs between genetically similar populations living in different areas, such as rural versus urban. Comparison of the faecal microbiota of elderly persons living in rural and urban areas in Japan showed that individuals living in Yuzurihara (a rural village) had a larger number of bifidobacteria, whereas larger proportions of bacilli and lecithinase-positive clostridia were found in residents of Tokyo[48].

By characterizing the gut microbiomes in rural cities of low IBD incidence, China offers unique insight into the potential protective role of a rural microbiome in IBD pathogenesis in Asia. Our ongoing country-wide investigation of IBD incidence in Asia reveals that Inner Mongolia has a lower IBD incidence than other regions (S.C.N., unpublished observations). Microbial profiling of Inner Mongolia residents indicates that the high-level presence of *Phascolarctobacterium*, *Lactobacillus* and *Bifidobacterium* might be related to a pasturing lifestyle and a dairy diet. *Lactobacillus helveticus* is frequently detected in individuals from every rural pasturing area in Inner Mongolia but not in Mongolians living in Hohhot city (urban), implying that diet affects the gut microbial composition of Mongolians[49]. Tyakht et al.[50] showed that microbial communities from residents in rural Russia had a 2.6-fold increase in the frequency of novel microbial community structures distinct from the common three enterotypes[51] compared with the microbial communities of urban hosts. The predominant microbial populations in rural populations were from the Firmicutes and Actinobacteria phyla. These bacterial communities are favoured by the consumption of starch-rich bread and potatoes, typical staple foods in rural Russia, and natural foods that are available to low-income socioeconomic groups from their household gardens[50,52,53]. Consistent with the theory of disappearing microbiota and its association with the emergence of chronic diseases[54], the frequently observed loss of microbiota richness and diversity during urbanization might largely account for the increase in IBD incidence. However, most of these studies were based on 16 S ribosomal RNA (rRNA) gene sequencing. An in-depth understanding of rural versus urban gut bacterial species or strains and

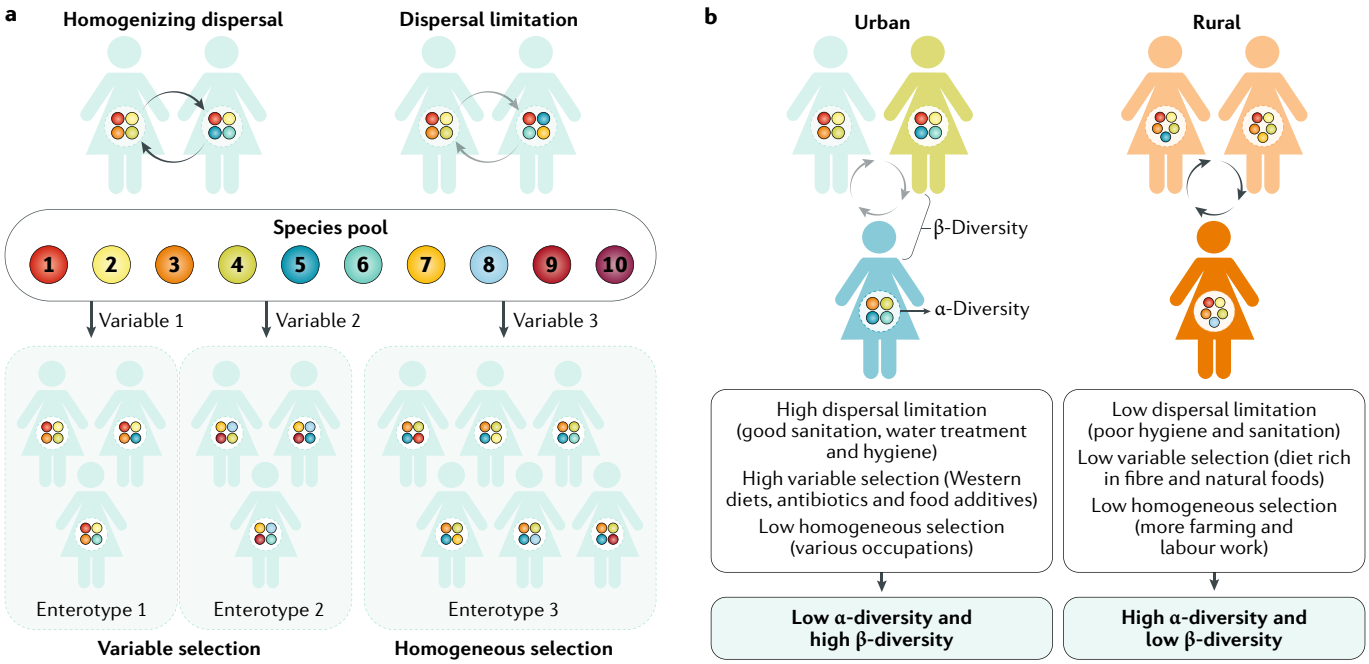

Fig. 1 | **Differential gut microbial community assembly scenarios in rural and urban settings. a** | The human gut microbial community assembly involves four processes[46,55,59]: dispersal (movement of organisms across space), selection (changes in community structure caused by deterministic fitness differences between taxa), diversification (generation of new genetic variation) and drift (stochastic changes in the relative abundances of different taxa within a community through time). Dispersal and selection are frequently observed to influence the gut microbial configuration during urbanization. Homogenizing dispersal results in similar community compositions among local scales owing to microbial transmissions vertically and horizontally, whereas dispersal limitation (for example, caused by improved hygiene measures) results in divergence in community composition in the context of limited exchange of microorganisms. Variable selection results when differences in selective environments (for example, diverse environmental variables) among local scales cause differences in community composition, whereas homogeneous selection results when a consistent selective environment among local scales causes community composition to be similar. Enterotypes here are referred to as different collections of diverse microorganisms in the gut. **b** | The human urban and rural gut microbiota assemblies in local communities are largely affected by constant microorganism dispersal and divergent variable selections. Lower dispersal caused by increasingly adopted hygienic measures and by less diversified natural environmental exposure and increased variable selections, such as increased use of antibiotics and consumption of industrialized products (such as, food additives) in the urban setting, might lead to a decrease of α-diversity in the urban gut microbiome. A combination of low homogenizing dispersal and low homogeneous variable selection results in an increased β-diversity in urban areas. By contrast, the microbiome of rural residents in local communities displays higher α-diversity and lower β-diversity than that of urban residents.

their functions in IBD pathogenesis is still lacking.

Microbial assemblies. By adoption of ecological theory, researchers have applied a new concept to studying gut microbial assembly in humans. A metacommunity encompasses the collection of microorganisms and an associated human population, whereby individuals represent local, island-like habitats occupied by spatially separated microbial assemblies linked through the transmission and dispersal of symbionts[55–58]. One rural–urban microbiome study interrogated the differences in the gut microbiota structure, diversity pattern and assembly processes between residents in Papua New Guinea (rural) and the USA (urban) based on metacommunity theory[46]. The faecal microbiota in residents of Papua New Guinea was found to be more diverse (α-diversity) but less individualized (β-diversity) than that of residents in the USA. Microbial diversity is shaped through processes of dispersal, selection, drift and diversification, with dispersal and variable selection postulated to play major parts[55,59] (FIG. 1). Homogenizing dispersal, which relates to horizontal microorganism transmission, was more influential on the presence or absence of the taxa in rural Papua New Guinea residents, whereas variable selection processes induced by broader cultural and genetic heterogeneity accounted for a higher diversity in the US residents[46]. Consistent findings from a similar analytical framework assembling bacterial ecosystems have been reported from individuals in Hadza and Italy[44,60,61]. Homogenizing dispersal predominates in the rural Hadza community, whereas a variable selection predominates in urban Italian individuals. The difference in bacterial microbiome assembly patterns in specific populations from rural and urban areas might be driven, at least in part, not just by diet but also by differences in sanitation and hygiene status. These data support the importance of dispersal in the assembly of the rural microbiome, suggesting that a diversified gut microbiota potentially protects the host against diseases, such as IBD, later in life.

Appropriate transmission of commensal intestinal bacteria between humans could promote health by establishing, maintaining and replenishing microbial diversity in an individual[62]. The diminished level of microbiota transmission during the process of urbanization, in both vertical (intergenerational) and horizontal (intragenerational) transmission, seemed to be associated with decreased gut microbiota diversity and richness[54]. Perhaps the combination of a loss of commensals in one generation due to aforementioned factors and the diminution of microbiota transmission gives rise to a fixed microbial depletion that becomes cumulative across

generations[54,63]. The increasing prevalence of Caesarian section worldwide and use of formula milk as a replacement for breast milk affects vertical transmission of the microbiota, whereas improved hygiene status during urbanization affects horizontal transmission of the microbiota; these factors have been shown to increase the risk of developing IBD[54,62,64–66]. However, caution should be taken when evaluating the effects of environmental factors on IBD pathogenesis. A meta-analysis of case-control studies with substantial heterogeneity found that breastfeeding was protective for both Crohn's disease and ulcerative colitis[66]. However, other studies have shown that breastfeeding is either a risk factor or has no association with IBD[67]. Further research is needed to clarify the direction of the association. Of interest, a multitude of environmental factors related to urbanization are associated with IBD development. For instance, in some studies, exposure to domestic refrigerators (indicative of a Western lifestyle and domestic hygiene) has been associated with an increased risk of Crohn's disease, as more patients with IBD were exposed to home refrigerators than controls[68–70]. One study reported an inverse relationship between poor oral health and IBD[71] and ectopic colonization of oral bacteria, such as strains of *Klebsiella* spp., in the intestine might drive T helper type 1 cell induction and inflammation[72]. In addition, ingestion of toothpaste was associated with increased risk of IBD, especially for Crohn's disease[70,73]. These studies underscore the association of various environmental factors with IBD incidence and the gut microbiota. As diet has also been shown to be one of the most important factors that affect the gut microbial composition, the next section focuses on studies related to this factor[74].

Diet and the gut microbiome

Western diet. A Western diet is loosely defined as one high in saturated fats, red meat and carbohydrates and low in fresh fruits, vegetables, whole grains, seafood and poultry. In both mouse and human studies, a Western diet has been shown to influence pathogenesis and/or development of a number of diseases, including IBD, cardiovascular diseases, hypercholesterolemia, obesity and diabetes mellitus[75–79], and in mice, a Western diet can induce transcriptomic and epigenomic reprogramming of myeloid progenitor cells, leading to increased proliferation and innate immune responses[80]. However, the role of rural or urban diets in IBD development remains less clear. To date, most of the evidence on the effect of urbanization and changes to the microbiota has been extrapolated from studies investigating the effect of Western diets in IBD development[78,81]. Long-term diet influences the structure, composition and function of the gut microbiota[82,83], but studies have also shown that short-term diet can alter the gut microbiome rapidly and reproducibly[84]. In rural inhabitants and hunter–gatherer societies, the diversity of the gut microbiota in individuals consuming an agrarian diet, which consists of more raw plant or fibre-based foods relative to a Western diet, was higher than that of Westerners on Western diet, ranging from one-tenth to onefold higher[43–46,85]. In mouse experiments, a decrease in bacterial diversity caused by diet or gene defects is associated with inflammation at the intestinal mucosal border, leading to autoimmune diseases and obesity[79,86]. In addition, a Western diet is associated with an increased susceptibility to adherent-invasive *Escherichia coli* (AIEC) infection[78]. The presence of AIEC in the gut has been reported to be associated with IBD pathogenesis[87–90].

One comprehensive review assessing the relationship between regional diet and global IBD incidence showed that an increased incidence of Crohn's disease significantly correlated with an increased consumption of animal products, honey, beer, animal fats and ghee[91], most of which are typical constituents of Western diets. In general, diet has been shown to influence the gut microbiota; however, one should be cautious when deciphering the association between diets and IBD pathogenesis, as the evidence for the role of different diets remains elusive, and many results are somewhat contradictory. Whether there is a direct influence of different diets on the gut microbiota in association with the changing incidence of IBD can only be clarified by mechanistic studies, which are currently lacking. Nonetheless, a diet low in fibre has been shown to be associated with a depletion of microorganisms in mice, which became more aggressive and irreversible over several generations[78]. The taxa driven to low abundances when dietary microbiota-accessible carbohydrates were low — for example, Bacteroidales, which are proficient in the consumption of dietary fibre — were inefficiently transferred to the next generation in mice[92,93]. Mice transplanted with gut microbiota from humans on a typical unrestricted American diet had an incomplete response (weak community reconfiguration and low-level alteration in the bacterial phylogenetic diversity) to a plant-rich, calorie-restricted diet with optimized nutrient intake (CRON), whereas mice transplanted with microbiota from CRON-consuming individuals were strongly responsive to both CRON and American diets[94]. These data suggest that the Western diet is associated with an irreversible gut microbiota dysbiosis. An increased response of the American-diet-associated microbiota to the CRON diet (increased bacterial phylogenetic diversity and community reconfiguration) was observed with bacterial dispersal between the hosts owing to the coprophagic nature of mice. This resulted in an influx of CRON-associated bacteria into the mice transplanted with the American-diet-associated microbiota, further supporting the hypothesis that bacterial dissemination in rural areas is an important factor for preserving the gut microbiota diversity in the host.

These findings potentially explain the effect of urban diets during industrialization on microbiome alterations and IBD development. In addition, a diet low in fibre has been shown to promote the expansion and activity of colonic mucus-degrading bacteria and colitis by enteric pathogens in mice[95]. In 2017, mouse studies showed that bifidobacteria or fibre protects against diet-induced microbiota-mediated colonic mucus deterioration[96] and that fibre-mediated nourishment of the gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health[97]. However, neither purified prebiotic fibres nor diet oscillations between fibre-rich and fibre-deprived diet alleviated degradation of the mucus layer in mice[95].

Dietary components. Dietary emulsifiers, such as carboxymethyl cellulose and polysorbate 80, which are widely used in processed food in industrialized regions, have been shown to promote colitis and metabolic syndrome via their effects on the mouse gut microbiota, which include potentiating bacterial attachment to and encroachment on the mucosa and altering species composition[98–100]. Furthermore, artificial sweeteners can induce dysglycaemia in humans and mice by altering the gut microbiota, reinforcing the glycan degradation capacity of gut microorganisms and increasing energy harvest and a number of pathways involved in sphingolipid metabolism and glucose transport[101]. Titanium dioxide nanoparticles, widely used as food additives or in pharmaceutical formulations, exacerbate dextran sodium sulfate

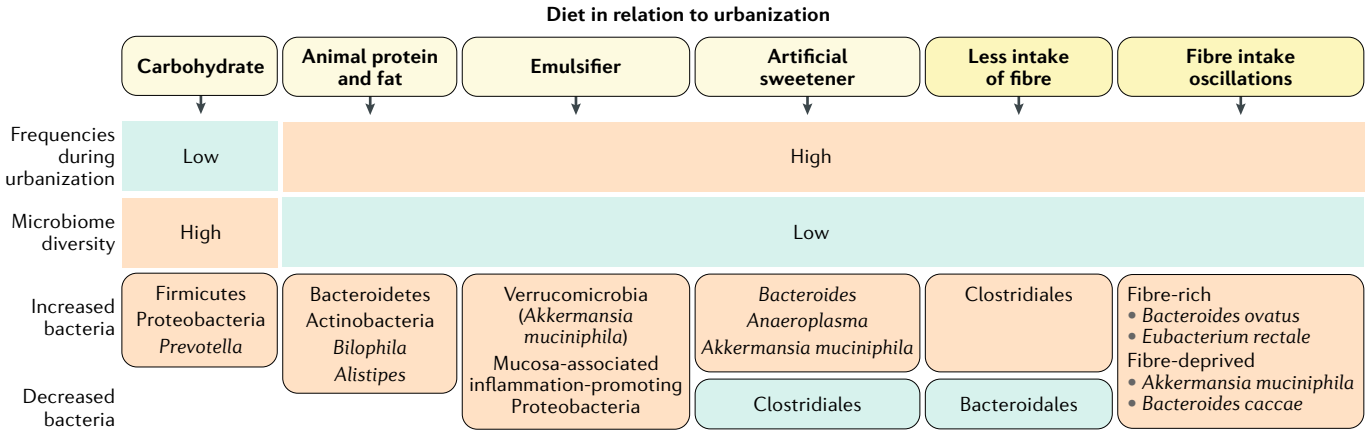

Fig. 2 | **Diet changes during urbanization and effects on the gut microbiota.** Urbanization is associated with a decrease in the intake of carbohydrates (including natural fibre) and an increase in the consumption of animal proteins, fats and food additives, such as emulsifiers and artificial sweeteners, all of which can lead to a diminished gut microbial diversity. The depletion of the microbial ecosystem caused by low fibre intake is transmissible over generations and becomes irreversible. Frequent dietary oscillations between fibre-rich and fibre-deprived diets in modern urban lifestyles have a detrimental effect on the gut microbiota. Processed fibre is not as protective as natural fibre to the diversity of the gut microbiota.

(DSS)-induced colitis in mice through a mechanism engaging the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome pathway[102]. Additionally, patients with IBD were found to have elevated titanium levels in blood[102]. These data highlight that a variety of food additives can alter the host–microbiota relationship, resulting in an unfavourable gut microbiome shift and potentially accounting for the emergence of Western diseases, including IBD.

Alterations in the *Prevotella*:*Bacteroides* ratio have been associated with certain diets in humans. A high intake of amino acids, dairy, lipids and cholesterol have shown to increase the abundance of *Bacteroides*[82], whereas *Prevotella* abundance is favoured by the intake of sugar and other complex carbohydrates[43,44,82]. Enrichment of *Bilophila* and *Alistipes* has also been ascribed to an animal-based diet[82,84]. In addition, an under-representation of *Bifidobacterium* has been observed in vegans from non-Westernized societies[82], which might be attributed to the absence of dairy products in their diet[44]. The gut microbiota adapts to a polysaccharide-rich diet, enabling the host to efficiently extract energy from dietary fibre while protecting from inflammation[103]. For example, high fibre intake in children from a rural African village in Burkina Faso exclusively enriches genera capable of cellulose and xylan hydrolysis, such as *Prevotella*, *Xylanibacter* (Bacteroidetes) and *Treponema* (Spirochaetes), which are absent in the microbiota of European children[43]. In addition to the loss of microbial species, the lack of microbiota-accessible carbohydrates required to fuel this community results in profound functional changes, such as decreases in short-chain fatty acid production[103]. A lack of dietary fibre intake associated with the development of IBD has been reported in epidemiological and animal studies[104–106]. Collectively, studies of the gut microbiome in association with urbanization have highlighted the potential importance of preserving a diversified microbiome via our diet (FIG. 2).

Antibiotics and the gut microbiome

In urbanized areas, large-scale medical and farming use of antibiotics is common[107]. In a study of schoolchildren from Shanghai, 21 common antibiotics, including human and veterinary antibiotics, were identified from urine samples[108]. Antibiotics have been shown to have a rapid and long-lasting effect, ranging from months to years, on the composition of the gut microbiome[109–114]. Broad-spectrum antibiotics have been shown to alter the abundances of 30% of the bacteria in the gastrointestinal tract and result in a rapid decrease in bacterial diversity, richness and evenness[111,112]. In the West, antibiotic use has been consistently shown to be an environmental risk factor for IBD[115], although a divergent protective effect for IBD has been reported in Asians and Middle Eastern migrants[30,116]. Childhood antibiotic use in developing countries might be a surrogate marker for exposure to infectious agents. In addition, antibiotic-induced dysbiosis might not occur as easily in developing countries, possibly owing to ubiquitous exposure to a diverse range of microorganisms that can rapidly repopulate the intestinal tract[117].

The effects of antibiotic-induced dysbiosis seem to be more long-lasting if they occur early in life, particularly in childhood, a pivotal period for immune system maturation and the establishment of immunological tolerance[118–120]. Changes in the intestinal microbiota caused by perinatal antibiotic exposure seem to programme the host to an obesity-prone metabolic phenotype that persists long term[121,122]. Although the cessation of antibiotics is associated with some microbial resilience and a return to a resemblance of the original state, this process might not be complete, and subtle or major changes in low-abundance organisms might, to date, have escaped characterization. Exposure to antibiotics can affect early-childhood microbiota owing to both the extent and timing of their use[54]. Antibiotics given to a mother during pregnancy or at birth (and even later, as they are excreted in breast milk) might have relayed effects on children through vertical transmission of the microbiota. In young children, antibiotic insults, from either prenatal events or direct medications, change the development of the gut microbiota and affect its normal maturation[54,119]. When elucidating the effect of antibiotics on IBD, a common confounder — defects in innate immunity — could cause both a later onset of IBD and childhood use of antibiotics owing to susceptibility to severe infections.

Microbiota dysbiosis has been associated with IBD and atopic and autoimmune diseases, and in some cases, these diseases are significantly associated with the intake of antibiotics during early life in both humans and mice[123–128]. One hypothesis is that repeated courses of antibiotics lead to

a loss of species, especially taxa that are low in number but have important metabolic functions for the host[110]. Epidemiological studies have shown that the incidence of Crohn's disease is increased in children who received antibiotics before 5 years of age[129].

Disruption of immune system development and maturation by altering gut microorganisms in early life might result in autoimmune diseases in later life[40]. In necrotizing enterocolitis (NEC), a low abundance of *Bifidobacterium*, accompanied by low bacterial diversity, has been detected before NEC onset[130,131]. Moreover, preterm infants exposed to antibiotics[132] and infants whose mothers received antibiotics prepartum[133] have a 20–40% increase in the incidence of NEC. In atopic diseases, several studies have demonstrated links to the composition of the gut microbiota during infancy and early childhood[134,135]. Consumption of broad-spectrum antibiotics in early life is also associated with asthma[136,137] and other allergic diseases[138].

Pollution and the gut microbiome

Air pollution is occurring in parallel with urbanization[5,107], and it is believed to have an increasingly detrimental effect on public health, including a rise in cardiovascular and respiratory diseases[139,140]. Exposure to air pollution has also been linked to gastrointestinal diseases, including IBD[141,142]. Long-term exposure to a high concentration of nitrogen dioxide and particulate matter has been associated with an increased risk of early-onset Crohn's disease, showing a linear increase proportional to high concentrations of pollutants[141].

Smoking, another form of inhaled environmental exposure, has been shown to increase the susceptibility to IBD via the alteration of the gut microbiota[143–146]. Pollutants might affect the physiology of the gut by modifying the gut microbial configuration and function. Van de Wiele et al. demonstrated in vitro that human intestinal bacteria have the capability to metabolize inorganic arsenic from contaminated soils to an array of toxic species[147]. In other studies, polycyclic aromatic hydrocarbons, incomplete combustion products of carbon-containing fuels found in urban-air particulates and in grilled and smoked meat, are transformed by the gut microorganisms into benzopyrene and compounds that exhibit oestrogenic properties in the body[148–150]. These findings highlight the role that the gut microbiota has in the bioactivation of environmental compounds, which might lead to disease development or the perpetuation of chronic diseases.

The gut microbiota can also metabolize other environmental chemicals, including nitrotoluenes[151,152], pesticides[153,154], metals[155–157], azo dyes[158] and melamine[159]. Inhaled pollutant particles alter the gut microbiota composition and function in mice[160]. When *IL10*$^{-/-}$ mice were given particulate matter in their diet, they showed marked changes in the relative abundance of Bacteroidetes, Firmicutes and Verrucomicrobia[160]. These alterations in microbial composition were associated with changes in short-chain fatty acids, whereby mice fed these particulate matters had increased production in the caecum of the branched-chain fatty acids, isovalerate and isobutyrate. Additionally, exposure of the gut to particulate matters resulted in a decreased concentration of butyrate. As butyrate is an essential fatty acid for colonocytes and mucosal immune cells, depletion in butyrate is frequently associated with a disruption in barrier function and increased propensity to mucosal inflammation[161]. These mice also showed a shift in the structure of the gut microbiome when exposed to polychlorinated biphenyls from contaminated foods[162]. These results suggest that ingestion of environmental pollutants substantially alters the gut microbiome and its metabolic functions. These alterations, in turn, can have detrimental effects on the structure and function of the intestinal mucosa, potentially leading to gastrointestinal diseases.

Mice fed cadmium-containing drinking water showed a marked decrease in nearly all the gut microbial species[155] and, in another study, heavy metal-consuming animals also had a lower abundance of *Lachnospiraceae* and a higher abundance of *Lactobacillaceae* and *Erysipelotrichaceae* compared with control animals[156]. A low level of *Lachnospiraceae* has been associated with intestinal inflammation and predisposition to colitis[163]. Data suggest that both changes in microbial colonization during the perinatal period and early-life exposure to environmental chemicals trigger dysregulated immune responses[164–166]. For instance, in utero exposure to methylmercury can decrease T cell functionality and alter circulating immunoglobulin levels in neonates[167,168]. Pollutants, such as aluminium, can otherwise negatively affect the intestinal barrier, decreasing the integrity of the barrier and mucosal healing, which leads to the exacerbation of colitis[169]. Thus, early-life exposure to chemicals might affect the composition of the enteric microbiota as well as host physiology.

The gut microbiota has broad enzymatic capacities and can metabolize environmental pollutants, thereby either increasing or decreasing the toxicity of chemicals to the mammalian host. Due to urbanization, more industrialized products are intensively being utilized, including agents for fluorescence, adhesives, spray paints, lacquers, inks, paint removers and cosmetics. These chemicals might also influence the composition and function of the gut microorganisms and could have effects related to IBD pathogenesis. Children born in urban settings are exposed to these environmental factors, which might affect their gut ecosystem and immune system from early life. In the next section, we further discuss early-life microorganism exposures in association with urbanization and IBD.

Early-life exposure

Microbial colonization. In 2017, a Canadian population-based inception and birth cohort study sought to determine the association of the risk of IBD with rural and urban residence in early life and found that rurality in the first 1–5 years of life was associated with a lower risk of IBD than urban residence (IRR 0.75–0.78)[170]. Microbial colonization of the gastrointestinal tract during early life plays an instrumental role in the development of the host immune system[40]. The mechanisms underlying how early-life microorganism gut colonization shapes the immune system are being studied and might provide further insight into the protective role of rural microbiota during childhood in IBD pathogenesis. During the first few years of life, immune maturation can be influenced directly and/or indirectly by the presence of commensal microorganisms[171,172]. Germ-free mice exposed to gut microbiota during adult life cannot achieve a similar transcriptional profile in the jejunum and colon as conventionally raised mice, whereas when colonized at an early age, they develop a phenotype similar to conventional mice[173,174]. A number of studies have revealed that early colonization with protective microorganisms might diminish the risk of developing autoimmune diseases, such as type I diabetes and allergic diseases[175,176]. These studies support the notion that early exposure to microorganisms might have a durable consequence in the host that extends into adult life[40]. In rural areas, residents are exposed to a more diverse microbial environment owing to lower sanitation conditions compared with urban environments[177,178]. One possible explanation for the higher incidence of IBD in

industrialized cities might relate to improved hygienic conditions causing the elimination of microorganisms within the naturally occurring indigenous intestinal microbiota that are important for educating the immune system[179–181].

Host immune system development. Early-life immunological development is also profoundly influenced by the inherited microbiota[54,182]. Several studies both in humans and in mice have demonstrated that the transmission of both microbiota and microbiota metabolites from a pregnant mother to the fetus helps shape neonatal immune development[182,183]. For example, germ-free mice born to transiently colonized mice have increased numbers of class 3 innate lymphoid cells in the small intestine and increased numbers of intestinal $CD11c^+$ $F4/80^+$ mononuclear cells in both the small and large intestine as compared with control germ-free pups[184]. Maternal microbiota-derived metabolites that reach the offspring are well exemplified by aryl hydrocarbon receptor ligands, short-chain fatty acids and retinoid compounds, all of which have been shown to have an effect on the development of the immune system[182,185]. Our own preliminary data in humans (MECONIUM study) showed a transmission of the gut microbiome from mother to child at birth[186]. Furthermore, babies born to mothers with IBD showed an enrichment in Gammaproteobacteria and a decrease in *Bifidobacterium* compared with babies born to control mothers, differences that persist at least for the first 3 months of life and suggest that maternal IBD status affects the gut microbiome composition of offspring, potentially contributing to future disease risk[186].

Further data underpinning the importance of early-life bacterial colonization are derived from studies of invariant natural killer T (iNKT) cell-mediated colitis in mice. These cells are a group of T cells that are defined by their ability to recognize self-derived and non-self-derived lipids in the context of CD1D, mediating host–microbial interactions and contributing to intestinal inflammation in human IBD[187]. Germ-free mice are hyperresponsive to environmental triggers that induce colitis in mice; this effect can be normalized through colonization with standard microbiota from wild-type mice, *Bacteroides fragilis* monocolonization or treatment with *B. fragilis*-derived sphingolipid antigens during the first 2 weeks of life but not thereafter[188,189]. *B. fragilis* modifies the homeostasis of host iNKT cells by supplementing the host's endogenous lipid antigen milieu with unique inhibitory sphingolipids, effectively dampening iNKT cell proliferation during neonatal development[188,189]. The protective effect of early-life colonization of *B. fragilis* against IBD also relies on microbiota-induced epigenetic changes of the *CXCL16* gene[188]. The effects of intestinal *B. fragilis* colonization are tissue-specific and restricted to the colon, strongly supporting the concept that specific microorganisms and derived molecules can distinctively regulate the immune system.

Acquisition of immune tolerance during the neonatal period can also be regulated by non-immune cells, such as intestinal epithelial cells (IECs). Toll-like receptor (TLR) signalling is specifically downregulated over the course of the first 2 weeks of life in mouse IECs but not thereafter[190,191], which renders IECs hyporesponsive to TLR stimuli, such as lipopolysaccharide (LPS) derived from Gram-negative bacteria. IECs in Caesarian-born neonates do not show decreased TLR signalling and are more prone to develop epithelial damage[191], suggesting an important role of specific types of microbial exposure in the development of epithelial tolerance during early life. These studies further emphasize that certain microorganisms acquired or developed in a rural environment might be involved in tolerance pathways establishment during early life.

Infections have been proposed as initiating factors for inflammatory disorders. More than 70% of people in the United States are estimated to experience a respiratory tract infection each year, and children, on average, have ten diarrhoeal episodes before the age of 5 years, which is dramatically higher in low-income to middle-income countries[192–194]. Modern urban societies are now burdened with endemic respiratory and gastrointestinal infections. Some insights were gained in mice studies that showed infections induce immune remodelling of the adipose tissue, infection-induced lymphatic leakage deviates migratory dendritic cell trafficking and that the microbiota plays a pivotal role in sustaining mesenteric inflammation and immune dysfunction in the long term after infection[195]. The immune remodelling phenotype following infection in mice was later extended to Crohn's disease-affected mesentery in humans; both macroscopic and microscopic features of Crohn's disease were observed following an acute infection, such as accumulation of creeping fat and disorganized lymphoid aggregates, analogous to that observed in mice[196]. These findings collectively indicate that persistent immune remodelling following clearance of acute infection in early or modern urban life might chronically lead to disruption of tissue-specific immune system, thereby contributing to the increased burden of autoimmune and inflammatory disorders, including IBD.

One study in 2016 characterized the infant gut microbiome from populations in Finland, Estonia and Russia, three environmentally disparate populations with different incidences of autoimmune diseases and economic standards. Marked differences were identified in the prevalence of specific intestinal microorganisms, such as *Bifidobacterium* and LPS-producing *Bacteroides* species[179]. LPS from specific constituents of early-life microbial communities in Finnish and Estonian subjects could stimulate (*B. dorei*-derived LPS) or actively inhibit (*E. coli*-derived LPS) endotoxin tolerance in later life. This observation indicates for the first time that immune education by certain microbial molecules, such as LPS, from rural microbiomes could affect long-term immunosuppressive mechanisms. By contrast, in the absence of appropriate or favourable microbial exposures in early life, especially in urban settings, the immune consequences might elicit irreversible and potentially deleterious effects in the host, thereby predisposing to IBD.

The non-bacterial gut microbiome

Owing to advances in high-throughput sequencing technologies, we are gaining new insights into the 'dark matter' of the gut microbiota, including the virome, mycobiome and parasitic helminths, extending the definition of the canonical 'microbiome'. These components of the gut microbiome are increasingly being perceived as important and might also relate to urbanization, but studies are currently lacking.

Virome. Over the past decade, the importance of the gut virome has been better understood using high-throughput sequencing technologies[197]. The virome (viral component of the microbiome), which is composed of both eukaryote infecting viruses and bacteriophages that infect bacterial cells, contains a more diverse genetic entity than the gut bacteria but has been much less extensively studied[198,199]. A healthy human gut virome is characterized predominantly by bacteriophages such as the double-stranded DNA Caudovirales and the single-stranded DNA *Microviridae*,

which latently infect their bacterial hosts and when under stress generate progenies that can infect and kill other bacteria[200–203]. In the absence of disease, gut bacteriophages exhibit substantial diversity between individuals and are temporally stable[200,202].

Bacteriophages have been proposed to be associated with IBD; however, their role in this disease remains largely undefined. There is a paucity of studies investigating the enteric virome in IBD[204,205]. No studies have compared the gut virome in rural or urban areas. In patients with Crohn's disease, a lower diversity but greater variability of the gut virome has been observed when compared with healthy controls[205]. Crohn's disease and ulcerative colitis have also been characterized by an increase in the richness of enteric virome in individuals from the United Kingdom and Chicago and Boston, USA[204]. Children with Crohn's disease have increased Caudovirales sequences in their intestinal washings and biopsy tissue samples compared with controls from patients with non-IBD[206]. Furthermore, more bacteriophage virions have been obtained in biopsy samples from patients with Crohn's disease than from healthy individuals using electron microscopy[207].

In 2016, one study demonstrated that a high-fat, high-sucrose Western diet can cause an enrichment of Caudovirales in obese mice[208], indicating a role for urbanization in the gut virome structure. Whether urbanization is a cause or consequence of virome alterations in IBD warrants further investigation. It has been documented that early-life colonization of certain viruses, such as norovirus, ameliorates intestinal abnormalities in germ-free mice and diminishes susceptibility to intestinal damage caused by chemical injury and bacterial infection[209]. Accordingly, some mucosa-attached viruses protect the underlying epithelium against bacterial infection via binding interactions between mucin glycoproteins and immunoglobulin-like proteins exposed on the phage capsid[210,211]. Whether rural environments contain viruses that can potentially educate or sensitize the host immune system, especially on the surfaces of inflamed and healthy mucosa or through factors affecting viral and bacterial colonization, is unknown.

Mycobiome. The fungal microbiome (mycobiome) has also been poorly studied in IBD. Although the functional importance of fungi in the natural ecosystem has been well recognized, comparatively little is known about their role in human physiology and IBD. It is unclear whether fungal alterations are affected by urbanization and its surrogates. The gut fungal microbiota has been shown to be altered in patients with IBD, which is characterized by an increased abundance of *Candida albicans*, an increased Basidiomycota:Ascomycota ratio and a decreased frequency of *Saccharomyces cerevisiae*[212]. Fungal diversity is also decreased in IBD[212]. In mice, gut inflammation promotes fungi proliferation[213], and certain fungi promote (*C. albicans*) or antagonize (*Saccharomyces boulardii*) host inflammation[214–217]. Long-term treatment with an antifungal drug such as fluconazole causes a fungal dysbiosis in mice, leading to an exaggerated host response to DSS-induced colitis[218]. Moreover, fungal-sensing genes *Card9* and dectin 1 are involved in innate immune responses and influence susceptibility to intestinal inflammation in both mice and humans[219–221].

Data are scarce regarding the delineation of rural and urban fungi configurations in IBD pathogenesis. Gut *Candida* is positively associated with diets high in carbohydrate in humans[208], indicating a potential effect of Western diet on the gut fungi composition. Although *C. albicans* is the dominant fungal species in most individuals, *Candida krusei* was found to be the predominant species in a remote population of Amerindian individuals[222]. This finding indicates that considerable heterogeneity might exist in the gut fungi composition between urban and rural societies.

Observations of decline in fungal diversity have been attributed to human activities typical of urban areas[223]; for example, atmospheric pollutants have been shown to alter ectomycorrhizal fungi in Europe[224], and effects on environmental fungi could further affect humans. For instance, fungal spores in urban indoor and outdoor air might cause allergic diseases, such as asthma, conjunctivitis and other autoimmune diseases[225,226]. Lichens are reported to be sensitive to nitrous oxides, sulfur and other pollutants and are used as bioindicators of air quality[227]. Sulfur pollution and heavy metals have also been shown to reduce species richness and change the community structure of phylloplane fungi[228]. This industrialization induces a loss of fungal biodiversity, and although it coincides with a downregulated gut fungal diversity in IBD, the relationship of the mycobiome to IBD pathogenesis remains to be clarified.

Airborne fungal spores and constituent fungal genera have been compared in rural and urban living environments[229–231]. In farmhouses, viable and total spore levels are 10^3 to 10^4 CFU/m^3 and 10^4 to 10^5 spores/m^3, respectively, which are 10-fold to 10^3-fold higher than the concentrations in urban apartments[229]. *Cladosporium*, *Aspergillus* and *Penicillium* spores exist in both urban and rural environments, whereas *Actinomyces*, *Acremonium*, *Alternaria*, *Botrytis* and *Chrysosporium* have been detected in farmhouses and cow barns but not in an urban environment[229]. These findings highlight a disparity in fungal composition between rural and urban environments.

Most of the comparative studies on rural and urban mycobiota have been restricted to targeted taxa because of enumeration measures, such as fungi culture assay and quantitative PCR. Rural and urban mycobiomes, and their association with IBD, should be explored further utilizing high-throughput sequencing technologies.

Helminths. In view of the lack of a consensus on the taxonomy of helminths, we have included enteric helminths in the broad term 'gut microbiota', as they co-reside in the gut with bacteria, viruses and fungi.

With greater urbanization and changes to the environment, the increasing incidence of IBD is accompanied by a decreased prevalence of helminth colonization[232]. Helminths play an important immunoregulatory role in the

Box 1 | **Open research questions and perspectives**

- What are the differences in the diversity (richness and evenness) of viral, fungal and helminth components of the human microbiota between urban and rural residents?
- What are the taxa (particularly at the species and strain level) that are differentially present between the gut microbiota of urban and rural residents, and what are their functional and mechanistic roles in IBD pathogenesis or host–microbiota symbiosis?
- How do differences in the environmental factors between urban and rural residencies (such as diet, hygiene, occupation and drug use) influence the gut microbiota configuration, accounting for the rapid increase in the incidence of Western diseases worldwide during urbanization, such as IBD and obesity.
- Does the gut microbiome of rural residents preserve more diverse and beneficial microorganisms, which are depleted during urbanization? If so, would a rural-associated microbiota be suitable for treating various Western diseases with faecal microbiota transplantation?

intestinal microbiota, and their absence has been associated with the development of IBD[232–234]. Ramanan et al. showed that helminth infection by *Trichuris muris* and *Heligmosomoides polygyrus* protects mice deficient in the Crohn's disease susceptibility gene *Nod2* from intestinal inflammation by inhibiting colonization of inflammatory *Bacteroides* species[220]. Decreased susceptibility to IBD in mouse models has also been shown with *Trichinella spiralis*[235,236] and *Schistosoma mansoni*[237] by modulating regulatory T cell (T_{reg}) expansion, *Trichuris trichiura*[238] by upregulating T helper cell type 22 response and *Heligmosomoides polygyrus*[239,240] by downregulating T helper cell type 17 responses in concert with expanding T_{reg} populations.

Helminth-colonized individuals have a higher microbial diversity than helminth-negative individuals among the indigenous Malaysian population[241]. Comparing individuals living in urbanized Kuala Lumpur with the rural Malaysian Orang Asli of the Temuan subtribe, the helminth-positive Orang Asli predominantly clustered in a group driven by the abundance of *Faecalibacterium* and *Prevotella*[234]. Those living in Kuala Lumpur fell into a second group characterized by *Bacteroides*[234]. This division in helminth prevalence and microbiota dominance between urban and rural populations supports the hypothesis that helminths might contribute to the differences in bacterial microbiome structure between rural and urban areas.

Helminth infections might also lead to anti-inflammatory mechanisms, including an increase in mucus and water secretion into the gut lumen[242,243]. Human trials in patients with IBD using pig whip worm (*Trichiuris suis*) have demonstrated clinical efficacy at ameliorating disease activities[244,245]. Whether there are specific endemic helminths residing in healthy individuals, especially in rural areas of lower IBD prevalence, that protect the host from the development of IBD remains unknown. There is a lack of population-based studies evaluating the role of gut helminths in rural and urban populations.

Conclusions

Urbanization is accompanied by an increased incidence of IBD. Diet, early-life microbiota exposure, changing hygiene status, pollution, socioeconomic status and other environmental factors have long-standing effects on the human gut microbiota and influence tolerance of the host to environmental exposures, perhaps potentiating the risk of IBD during urbanization. However, there are limitations of the current bacterial microbiota analysis techniques. Most data are based on 16S rRNA gene sequencing, which might provide an incomplete and biased insight into the gut microbiota composition. A reduction in microbial diversity according to indices of analysis for 16S rRNA sequences (such as the Shannon index) is merely a mathematical construct, which indicates an imbalanced gut ecosystem but does not provide us with more detailed information regarding the strains (species or taxa) and functions of certain microorganisms. Overall, there is also a lack of functional studies. Thus, large-scale metagenomics, metatranscriptomics and functional studies are needed for investigating the roles of the gut microorganisms in the molecular pathogenesis of IBD.

As the gut microbial ecosystem is reflective of external environmental triggers, studies of the gut microbiota in rural and urban residents could shed light on the pathogenesis of IBD and provide therapeutic insights into IBD treatment (BOX 1; FIG. 3). Rapid industrialization and increasing incidence of IBD in some of the newly industrialized countries within populations of homogeneous ethnicity have highlighted a remarkable difference of the gut microbiota in urban and rural areas. An understanding of which components of the gut microbiota and which risk factors are important in IBD pathogenesis might lie in this rural–urban dichotomy.

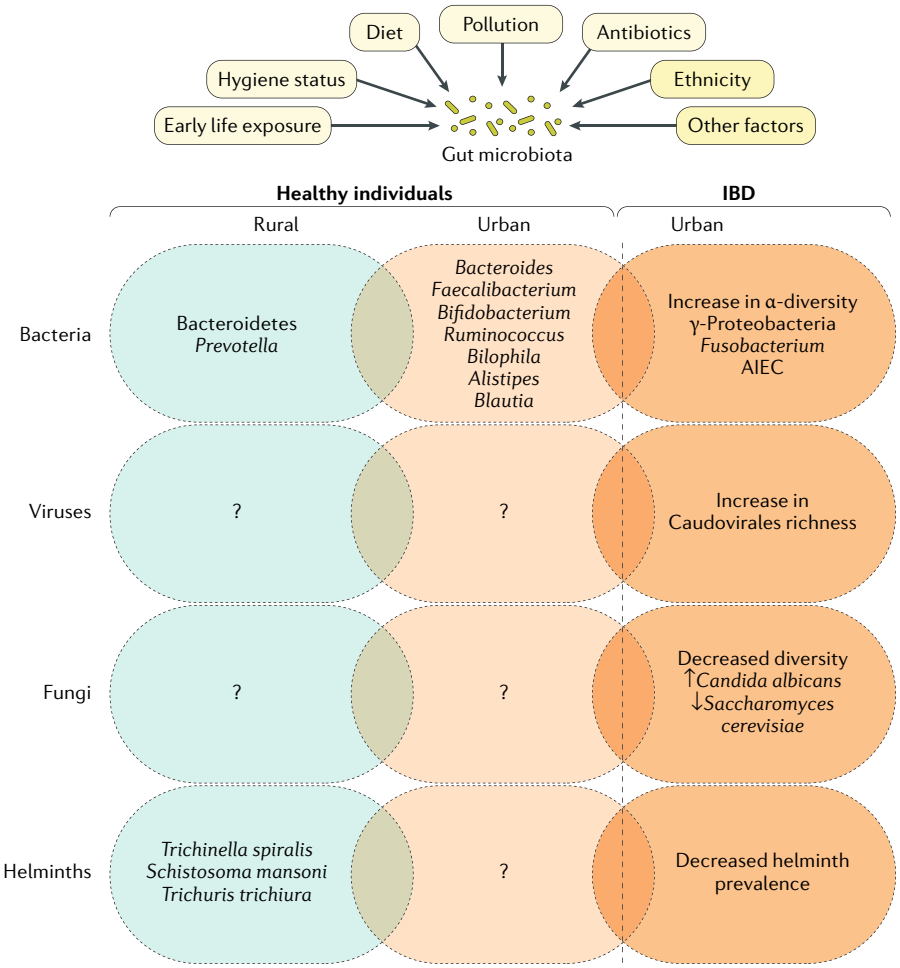

Fig. 3 | **The changing landscape of the gut microbiome during urbanization and its relation to IBD.** Concomitant with urbanization, the incidence of IBD is increasing rapidly, particularly in developing nations. Diet, early-life exposure, hygiene practices, ethnicity and other environmental factors all have long-standing consequences for human gut microbiota, thereby potentially affecting host susceptibility to IBD. Although gut microbiota characteristics in IBD have been revealed, unravelling the discrepancies in rural versus urban gut microbiomes might provide further insights into the aetiology of IBD pathogenesis and IBD therapeutics. To date, little is known about the rural and urban microbiomes underlying IBD pathogenesis, particularly when taking into account microbiome variabilities caused by ethnicity and subsistence mode. AIEC, adherent-invasive *Escherichia coli*.

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