Our Health and Environmental Microbial Biodiversity
The Health Benefits of Green Space — Psychology or Biology?

Text and images by Graham Rook

"I shall soon be rested," said Fanny; "to sit in the shade on a fine day, and look upon verdure, is the most perfect refreshment." —Fanny Price, in Chapter 9, *Mansfield Park*, by Jane Austen, published in 1814

Introduction

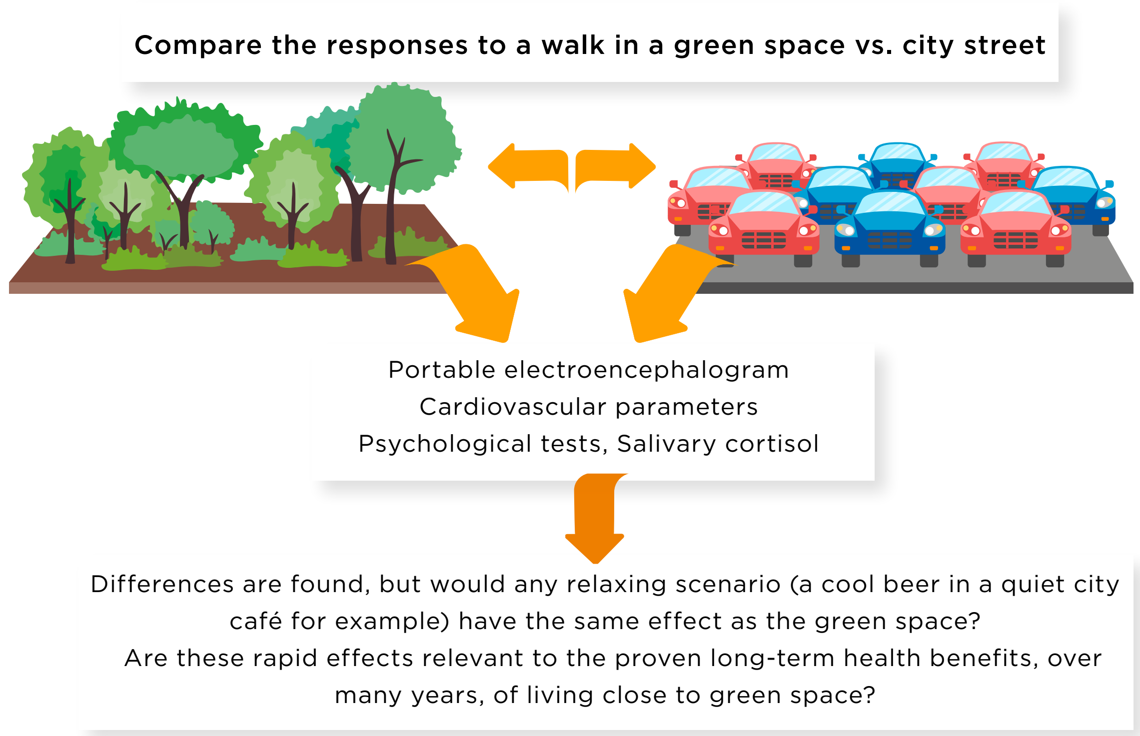
We all accept the notion that exposure to the natural environment or to gardens and parks can be beneficial. Indeed, large epidemiological studies demonstrate that living close to natural rural or coastal environments, often denoted "green space" or "blue space" respectively, reduces overall mortality, cardiovascular disease, and depressive symptoms and increases subjective feelings of well-being (Maas et al. 2006; Mitchell and Popham 2008; Wheeler et al. 2012). These beneficial effects are particularly prominent in urban individuals of low socioeconomic status who tend to be most severely deprived of green space (Maas et al. 2006; Mitchell and Popham 2008; Dadvand et al. 2012; Wheeler et al. 2012).

If asked why these effects occur, most people would implicate relaxation, sun, and exercise. However, recent work suggests that the answer is more complicated than that. Here, I will first explain the information gaps in the current concepts, then introduce a new candidate: exposure to microbial biodiversity, which is rendered essential by our evolutionary history and by the workings of our immune systems. This issue is important because the more we understand the mechanisms of the health benefits of green space, the more efficiently we can exploit them for human well-being.

Some protagonists of the view that the benefits are due to psychological mechanisms tend to quote the rapid psychological and physiological changes that can be demonstrated after short exposure to parkland and forests. This rapid effect can be proven not only by psychological testing (Berman, Jonides, and Kaplan 2008), but also by mobile electroencephalograms (Aspinall et al. 2013) and by measurements of cerebral blood flow, various cardiac parameters, blood pressure, and salivary levels of the stress hormone cortisol (Tsunetsugu, Park, and Miyazaki 2010; Park et al. 2010). But there are two major uncertainties about the relevance of this work (See Fig. 1). First, there is the issue of specificity. In addition to comparing exposure to a green space with exposure to a busy city street, it would also be useful to compare it with other relaxing environments, such as a quiet comfortable inner city café or videos of cute kittens. The second problem is the absence of evidence that the measurable rapid short-term psychological and physiological changes that follow exposure to natural environments (whether specific to such environments or not) translate into long-term health benefits. In other words, are these immediate short-term effects related to the long-term health benefits of living close to green space over many years, such as reduced mortality, cardiovascular disease, chronic inflammatory disorders, and depression (De Vries et al. 2003; Maas et al. 2006; Maas et al. 2009; Mitchell and Popham 2008; Wheeler et al. 2015) or are they more transient in nature?

So although these psychological effects unquestionably exist, we do not fully understand their role. It is likely that the relaxation and satisfaction derived from the natural environment represents the equivalent of "habitat selection" in other species (Morris 2011). As shown recently by analysing carbon isotopes in tooth enamel, from as early as three to four million years ago, hominins were evolving in wooded grassland (Sponheimer et al. 2013), and they followed rivers and coastlines or settled near lakes. Thus humans will have evolved to obtain psychological rewards from approaching these ideal hunter-gatherer habitats (Frumkin 2001). So contemplating green space certainly makes us happy and relaxed. In the later part of this article, I will discuss if this is why it also make us healthier and prolongs our lives.

The other suggested benefits (sunlight, social interaction, exercise) are neither specific nor exclusive to green space. Sunlight is thought to counteract Seasonal Affective Disorder (SAD) (Rosenthal et al. 1984), and access to green space might promote social interactions and a sense of community (Kuo et al. 1998). Green spaces sometimes encourage physical activity (Maas et al. 2008), though city-dwellers can walk to most resources and tend to do so, whereas individuals living in rural suburbs are often forced to use their cars to get anywhere, so exercise can paradoxically decrease (Oakes, Forsyth, and Schmitz 2007). In fact, recent analyses of the large studies in the United Kingdom and the Netherlands indicate that although exercise is certainly beneficial, it is *not* the explanation for the



1. Many publications compare rapid psychological responses to a walk in a city street with responses to a walk in a green space. But without controls, the findings are difficult to interpret. The key questions are shown at the bottom of the figure.

health benefits of green space (Maas et al. 2008; Lachowycz and Jones 2014). Current available data has not even been able to determine whether exercise taken in a green space is more beneficial than exercise taken in a city gym (Thompson-Coon et al. 2011). Another possibility is that proximity to green spaces correlates with less exposure to traffic pollution, but a recent study has found that reduced pollution only explains a small part of the observed benefits (Dadvand et al. 2015).

Summarising the previous paragraphs, we know that living close to the natural environment has long-term health benefits (Maas et al. 2006; Mitchell and Popham 2008; Wheeler et al. 2012). These benefits might be an additive consequence of several effects, including an evolved psychological need, plus perhaps exercise, sunlight, social interactions, and reduced pollution levels, but there are no conclusive data (Rook 2013). This issue is crucial because urban planners need to know the mechanisms of the beneficial effects of urban green space so that the health advantages derived from green spaces can be optimised.

The Health Problems of Modern Urban Life

So what are the health problems that arise in high-income urban communities that might be alleviated by access to green spaces? Urban communities are undergoing large increases in the prevalence of chronic inflammatory disorders such as allergies, autoimmune diseases, and inflammatory bowel diseases (Bach 2002). All of these are at least partly disorders of the mechanisms that stop the immune system from causing unnecessary inflammation. In allergic disorders, the immune system attacks harmless allergens in the environment or food. In autoimmune disorders, such as Type 1 diabetes and multiple sclerosis, the immune system attacks one's own organs, and in inflammatory bowel diseases, it attacks the gut contents.

In high-income urban communities, there is also an increase in diseases associated with long-term background inflammation occurring in the absence of detectable medical cause. This is easily monitored by measuring blood levels of biomarkers of inflammation such as C-reactive protein (CRP). Persistent background inflammation is associated with cardiovascular disease, metabolic syndrome, insulin resistance, obesity (Goldberg 2009; Shoelson, Herrero, and Naaz 2007), low stress-resilience, depression (Valkanova, Ebmeier, and Allan 2013; Rook, Raison, and Lowry 2014; Gimeno et al. 2009; Khandaker et al. 2014), and post-traumatic stress disorder (Eraly et al. 2014). Finally, some cancers that are increasing in high-income settings are also associated with poorly controlled inflammation (for example, colorectal, breast, prostate, classical Hodgkin's lymphoma, and acute lymphatic leukaemia of childhood) (Rook and Dalgleish 2011; Von Hertzen, Joensuu, and Haahtela 2011).

We've seen that in high-income urban communities, the immune system makes two types of mistakes. First, it attacks things like our own tissues that it should not attack, and second, it fails to turn off background inflammation when it is not needed. This is a concern as inflammation is metabolically costly and, in the long term, dangerous.

Why Are Urban Immune Systems Prone to Overactivity?

Why is the modern urban immune system functioning incorrectly? At birth, the immune system is like a computer that has hardware (structural components) and software (genetic programmes), but almost no data (See Fig. 2). In order to function correctly, the immune system must acquire these data, preferably during the early years of life. The sources of the data are the various classes of microorganisms with which humans co-evolved. So what are these microorganisms, and why are they now absent or depleted such that our immune systems do not have all the data they need?

Our Symbiotic Microbial Partners

We tend to think of humans as individuals. In fact, humans, like all vertebrates, are ecosystems. We are hosts to a huge and diverse community of microorganisms (the microbiota), particularly in the gut. Only about 10 percent of our cells are human, and less than 1 percent of the genes that influence our development, physiology, and health are situated in the human genome inside our human cells. Most of "our" genetic material is located in the organisms that constitute our microbiota. This microbiota, notably the gut microbiota, influences the development of most, or perhaps all, of our organ systems (McFall-Ngai et al. 2013; Gilbert, Sapp, and Tauber 2012). For example, in germ-free animals artificially created by caesarean section in sterile laboratories, the brain fails to develop normally, and human experiments have shown that the gut microbiota influences aspects of cognition involved in emotion and sensation (Tillisch et al. 2013). Similarly, we now know that there is a critical period during infancy when the composition of the microbiota determines the long-term function of the immune system and the balance of metabolic pathways. If the microbiota is defective at this critical time (for example, due to heavy antibiotic consumption), the animal grows up with a tendency to inflammation and obesity—which are crucial correlates of malfunction of these two systems (Cox et al. 2014).

Loss of Biodiversity: Consequences for Human Health

It is not only in childhood that the composition of the microbiota is important. Gut microbiota of abnormal composition, or of limited diversity, is characteristic of conditions associated with human inflammation (Turnbaugh et al. 2009; Rehman et al. 2010) and often associated with poor control of inflammation in experimental animals (Hildebrand et al. 2013). Similarly, diminished microbiota biodiversity in institutionalised elderly people correlates with raised levels of markers of inflammation in the blood and declining health (Claesson et al. 2012). So the microbiota is essential not only for the development of our organs, but also for their continuing healthy function.

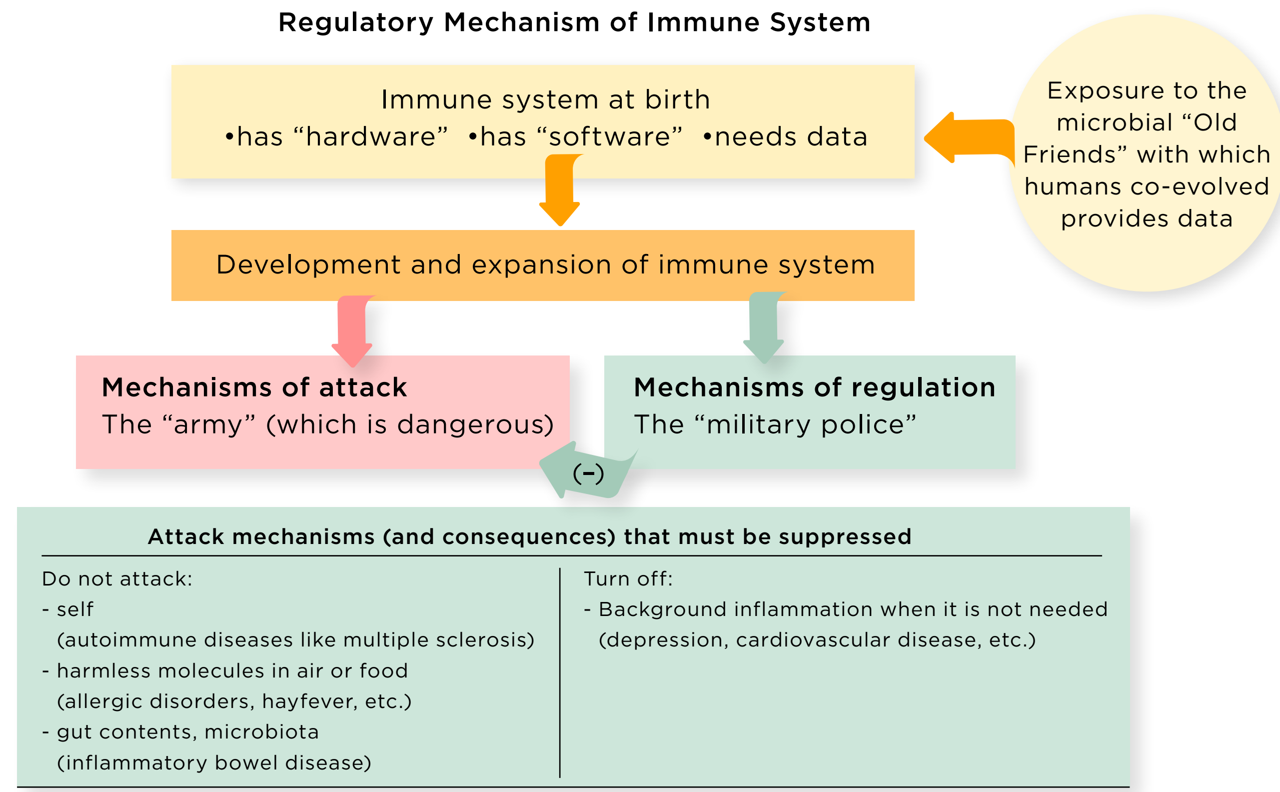
Where Do Our Microbiota Come from, and What Goes Wrong in Cities?

Humans and other mammals initially obtain many of the microorganisms that constitute their microbiota from their mothers' faecal and vaginal microbiota during delivery, and via breast milk, which is not sterile (Jost et al. 2013), and from family members. In fact, breast milk contains "prebiotics". These are polysaccharides that cannot be metabolised by the baby, but are present in the breast milk to nourish and encourage certain types of bacteria in the infant gut (Garrido, Barile, and Mills 2012). Interestingly, the prevalence of allergic eczema is reduced in babies whose mothers suck the pacifier (dummy) clean after it has fallen on the floor then place it in the baby's mouth, compared to the incidence in those whose mothers provide them with a new sterile one (Hesselmar et al. 2013). Many modern behavioural practices tend to limit this crucial transfer of microbiota from the mother to the baby. Caesarean delivery, lack of breast-feeding, antibiotics (Rook, Raison, and Lowry 2014), and increasing uniformity of diet (Khoury et al. 2014) all aggravate the problem.

However, the mother is not the only source of microbiota. Many, or probably all, animal species including humans obtain components of their microbiota from soil and the natural environment (Troyer 1984; Mulder et al. 2011). It is very probable that geophagy (or the eating of earth) by babies and infants is an evolved strategy for the uptake of soil organisms. This is manifested as the "oral" phase of development, when all babies put whatever they can reach into their mouths. The quantities of soil and faecal matter that can be ingested by human babies with access to these materials (for example, in an African village) are astonishing (Ngure et al. 2013).

Health Benefits of Exposure to Farms and Farmland

Soil is not the only non-maternal source. Evidence that humans acquire important microbial biodiversity from the environment comes from studies of the effects of contact with farms, animals, and green spaces. Exposure of the pregnant mother or infant to the farming environment protects the child against



2. The immune system is like the brain. It needs to learn. The data that it requires to function correctly come mostly from exposure to microorganisms. This data input trains regulatory mechanisms that stop inappropriate activity of the immune system. If not regulated by these mechanisms, the immune system is dangerous.

allergic disorders and juvenile forms of inflammatory bowel disease (Riedler et al. 2001; Radon et al. 2007). This protection appears to be attributable to airborne microbial biodiversity that can be assayed in children's bedrooms (Ege et al. 2011). Similarly, mere proximity to agricultural land rather than urban agglomerations increased the biodiversity of skin microbiota, reduced atopic (or allergic) sensitisation, and increased the release of IL-10, an anti-inflammatory mediator, by blood cells (Hanski et al. 2012).

Health Benefits of Exposure to Animals in the Environment

Some of the relevant microbiota come from animals. Contact with cows and pigs protects against allergic disorders (Riedler et al. 2001; Sozanska et al. 2013). Contact with dogs, with which humans have co-evolved for many millennia (Axelsson et al. 2013; Thalmann et al. 2013), also protects from allergic disorders (Ownby, Johnson, and Peterson 2002; Aichbhaumik et al. 2008), and people share their microbiota via dogs (Song et al. 2013), which greatly increase the microbial biodiversity of the home (Fujimura et al. 2010; Dunn et al. 2013). In a developing country, the presence of animal faeces in the home correlated with better ability to control background inflammation in adulthood (McDade et al. 2012). In Russian Karelia, where the prevalence of childhood atopy is four times lower, and that of type 1 diabetes is six times lower, than in Finnish Karelia, house dust contained a seven-fold higher number of clones of animal-associated species than was present in Finnish Karelian house dust (Pakarinen et al. 2008).

Gut Microbiota in the Green Environment

Another fascinating issue is the role of spore-forming bacteria that are usually considered to be soil organisms, but which can germinate and replicate in the human gut (Hong et al. 2009; Rook, Raison, and Lowry 2014). About one-third of the species that constitute the human gut microbiota are spore-forming. Spores are astonishingly resistant and can persist in the environment for tens of thousands of years. So wherever humans (or other vertebrates) have been in the past, gut-adapted microbial strains have been seeded into the environment via faeces and are waiting there as spores, ready to be picked up by newly arriving humans and soil-eating babies! We do not currently know how much of the human microbiota is derived from the microbial environment, though work on this point is in progress, and the overlaps between gut and soil or plant root microbiota have been discussed (Ramérez-Puebla et al. 2013). Germ-free mice readily develop a functioning gut microbiota following exposure to microbial communities from soil (Seedorf et al. 2014).

The Green Versus the Built Urban Environment

Compared to the green environment, the microbiota of the modern built urban environment is not only different in composition, but also of reduced biodiversity (Kembel et al. 2012; Ehrenberg 2015). So we need exposure to the green spaces in which we evolved. As one might expect, the gut microbiota of American citizens is different from that of Amerindian hunter-gatherers living in a green environment and strikingly less biodiverse (Yatsunenko et al. 2012). As outlined in the introduction, exposure to green spaces reduces overall mortality, cardiovascular disease, and depressive symptoms. It also increases subjective feelings of well-being (Maas et al. 2006; Mitchell and Popham 2008; Dadvand et al. 2012; Aspinall et al. 2013) and cognitive development in children (Dadvand et al. 2015). Similarly, exposure to agricultural environments protects us from some forms of inflammatory bowel disease and allergies (Riedler et al. 2001; Radon et al. 2007; Hanski et al. 2012). In the latter cases, the mechanism has been studied, and there are clear indications that the effect operates via the immune system (Schaub et al. 2009; Hanski et al. 2012) and these protective effects are readily reproduced in experimental animals. Unfortunately, there has been no investigation of the mechanism of the earlier green space epidemiological studies. But since we know that all of these conditions can be caused or aggravated by the poor regulation of the immune system, chronic inflammation, or inappropriate microbiota, it now looks very likely that an important function of green space (and of the soil and animals within it) is to provide exposure to microbial biodiversity that supplements the microbiota and provides data to the immune system. The farm effect and the green space effect are likely to be the same.

Some particularly relevant experiments have been performed with piglets, showing that when maintained with the sow in a field, they developed gut microbiota that was very different from that of piglets maintained with the sow on the same diet, but in a clean indoor environment. But even more important, biopsies of the gut epithelium of the indoor piglets revealed increased activity of genes that drive inflammation (Mulder et al. 2009). Moreover, these indoor piglets, deprived of exposure to the natural environment, had reduced numbers of the cells that constitute the "police force" of the immune system (regulatory T cells), with the crucial role of stopping inappropriate inflammation (Lewis et al. 2012). Moreover, to strengthen still further the parallel with the life of high-income modern urban babies, the indoor piglets mounted an inappropriate immune response following introduction of a novel food (soya milk). In other words, the indoor piglets were developing food allergy. This represents an elegant model of the way that human babies are reared in high-income settings, with minimal contact with environmental biodiversity, and parallels the rising incidence of food allergies and other immunoregulatory abnormalities in such babies.

Horizontal Gene Transfer

In addition to the exchange of whole organisms with animals and the natural environment, we need to consider horizontal gene transfer (Smillie et al. 2011). This is common between bacteria, and recent work has revealed the existence of a global network of horizontal gene transfers between members of the human microbiota, even between phylogenetically very divergent bacteria separated by billions of years of evolution. Horizontal gene transfer also plays essential beneficial roles because it further increases the flexibility of human physiology. The genomes of our own human chromosomes are fixed, but the genomes of our symbiotic microbial partners are not, so we have a mechanism for adapting to new environments and diets. Consumption of seaweed by Japanese people induces horizontal transfer to their microbiota from environmental microbes of genes that enable the catabolism of novel seaweed-associated carbohydrates (Hehemann et al. 2012). Thus the adaptability of humans depends upon appropriate contact with potential sources of genetic innovation and diversity, and might therefore be threatened by loss of biodiversity in the gene reservoir of environmental microbes.

Quantities of Microorganisms in the Air We Breathe

Does exposure to the green environment result in an uptake of physiologically relevant quantities of organisms? The answer is a definite yes. Particulate matter in the air, such as pollen and plant fragments, carries a load of bacteria (Heydenreich et al. 2012). Many airborne particles are more than five-millimetres-large and will therefore be deposited in the upper airways, together with organisms that come mostly from soil and plants. They can have local pharmacological or immunological effects in the airways (Moore 2015), but after being carried up the trachea by the action of cilia, they will then be swallowed and can also exert additional effects via the gut.

When total numbers of organisms in air were counted, levels of 10^5 per cubic metre or more were regularly encountered over a grassy field on clear sunny days, and estimates approaching 10^6 per cubic metre have been reported above shrubs and some grasslands (Burrows et al. 2009). The air in facilities housing agricultural animals can contain still higher numbers, reaching 10^7 to 10^8 microorganisms per cubic metre (Nehme et al. 2009). Clearly the volume of air breathed by a human depends on the degree of exertion. The average is

Mechanisms of Green Space Health Benefits

Biological		Psychological
Need for diverse microbial input to immune system	Walk in green space	Psychological need (habitat selection)
Increase microbial load & biodiversity in home	Dogs	Psychologically rewarding companion
Microbial biodiversity	Farming environment	Less stressful lifestyle
Exchange of microbiota	Social interaction	Build social capital
Vitamin D improves regulation of immune system	Sunlight	Combat Seasonal Affective Disorder
More immunoregulation	Exercise	Health benefits, weight loss

3. Why is green space good for our health? In addition to the probable psychological mechanisms, green space provides microbial biodiversity to the symbiotic microbiota and inputs of data that improve regulation of the immune system, as described in Fig. 2. Moreover, other factors associated with exposure to green space such as exercise and sunlight also increase the efficiency of immunoregulation.

about 11 cubic metres per day, but at maximum exertion, this volume could be as high as 90 cubic metres per day. So a crude calculation suggests that humans, depending on how and where they are living, can breathe in anything from about 10^6 to almost 10^{10} environmental organisms in 24 hours, many of which are associated with larger particles that will lodge in the mucus of the airways. This is more than enough for pharmacological and immunological effects (Moore 2015). Values at the higher end of the range will have been the norm during our hunter-gatherer evolution.

Conclusion

In conclusion, exposure to green spaces and the natural environment has short-term psychological effects and long-term health benefits, including an overall reduction in mortality and a reduction in inflammation-associated disorders. The mechanism of the long-term effects has really only been investigated in the context of exposure to farms or living close to agricultural land. These studies have shown that the long-term effect is mediated in part via the immune system, in partnership with the microbiota (Rook 2013). The immune system requires exposure to microbial biodiversity in order to function correctly. These effects are no doubt supplemented by other factors, such as relaxation, sun, and exercise.

The wonderful parks of Singapore must be beneficial, but if we understood more about the precise composition of the microbial biodiversity that we need, perhaps the benefits of these parks could be increased still further. Many effects of green space that are usually assumed to be psychologically mediated are just as easily explained by mechanisms operating via the immune system (See Fig. 3). The better we understand these interactions, the better we will be able to modify the urban environment for the benefit of human health.

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