



# Biodiversity hypothesis explaining the rise of chronic inflammatory disorders – allergy and asthma among them – in urbanized populations?

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## ABSTRACT

Human commensals are no longer seen as passive bystanders or transient passengers, but rather and increasingly as active and essential participants in the development and maintenance of the barrier function and immunological tolerance. A suddenly reduced abundance or diversity of these microorganisms, previously ubiquitous, may have led to failures in regulating and restoring appropriate immune and inflammatory responses. Evidence indicates that alterations in the indigenous microbiota correlate with inflammatory disease states, and it is well known that inflammation is a cardinal feature of clinical conditions, including asthma and allergic diseases, autoimmune diseases, and many forms of cancer. This review focuses on the novel “biodiversity hypothesis”, which could be regarded as an extension of the hygiene hypothesis and microbial deprivation, or microbiota hypothesis. According to this hypothesis, population growth (urbanization) leads to loss of biodiversity (poor macrobiota/microbiota), poor human microbiota (dysbiosis), immune dysfunction (poor tolerance), inflammation, and finally clinical disease.

**Keywords:** Biodiversity hypothesis, microbiota, immune tolerance, asthma, allergic diseases, inflammation.

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## INTRODUCTION

More and more people around the world are living in cities and experiencing little contact with nature. This is significant for public health, because contact with natural environments rich in species seems to be strongly related to the presence of beneficial protective bacteria on the human barriers (skin, gut and airways) and consequently with immunotolerance.

An ever-growing proportion of populations suffer not only from allergies and asthma but also from other chronic inflammatory diseases, obviously as a result of mismatched immunological mechanisms and adaptation to modern urban life. Environmental micro-organisms, previously ubiquitous and abundantly present e.g. in drinking water and milk, are key players for the induction

and maintenance of immunoregulatory circuits and tolerance.

### KARELIA ALLERGY STUDY

In the Karelia area, northeastern Finland, we found that environmental biodiversity, human microbiota and allergy are interrelated.<sup>1</sup> We studied 118 randomly selected teenagers from northeastern Finland. The participants were screened to identify those who were and were not sensitive to a range of common allergens. In addition, skin swabs were taken from the forearm of all the participants to identify the composition of the skin microbiota (which bacteria were living on their skin). The environment surrounding the homes of the participants was recorded, including the identification of common and uncommon plant species in the yard.

Participants who lived on farms or near forests had a different composition of bacteria on their skins and were less sensitive to allergens than those who had less contact with the natural environment and were living in built-up areas or near lakes and other water bodies.

The study suggested that contact with biodiverse natural environment *with abundant bacteria* and probably with other microbes, can protect people from becoming sensitized to allergens, by building up the immune system. In particular, the sensitivity of teenagers to allergens appeared to be linked to diversity of plants around the home. The surroundings of healthy participants contained 25% more uncommon native flowering plant species than the surroundings of allergen-sensitive participants. This was the case even after taking into account the effect of possible confounding factors.

Healthy teenagers had a greater diversity of one group of bacteria, in this case gammaproteobacteria, on their skin compared to teenagers who were more sensitive to allergens. In addition, among healthy teenagers the abundance of certain gammaproteobacteria, *Acinetobacter*, on the skin was positively associated with the level of an important anti-inflammatory signalling molecule, interleukin-10, in the blood.

These results imply that a high genetic diversity of gammaproteobacteria on the skin is linked to increased tolerance against allergens. Gammaproteobacteria are found in the environment, such as in the soil, on plant surfaces, on grass pollen, and on dust, and may be more diverse in the natural environment than in the urban environment.

### CONCEPTS OF BIODIVERSITY

By definition, biodiversity is 'the variability among living organisms from all sources, including, *inter alia*,

terrestrial, marine and other aquatic ecosystems and the ecological complexes of which they are part. This includes diversity within species, between species and of ecosystems'.<sup>2</sup> In practice, the key elements of biodiversity include genetic diversity of populations and species; the richness of local and global species; the spatial extent and the state of natural habitats; and the functioning of ecosystems that provide various essential services to mankind.

Although the Convention of Biological Diversity<sup>2</sup> is primarily concerned with plants and animals, biodiversity also includes micro-organisms, which are less visible but comprise the bulk of living matter on our Earth.<sup>3</sup> Biodiversity, according to the definition, concerns both environmental and commensal microbiota.

We have proposed that biodiversity at the level of macrobiota and microbiota are interrelated in that biodiversity loss of the former is likely to be associated with loss of diversity of the latter.<sup>4</sup> Moreover, biodiversity loss leads to reduced interaction between environmental and human microbiotas. This in turn may lead to immune dysfunction and impaired tolerance mechanisms in humans.

The rate of biodiversity loss does not show signs of slowing down, and worryingly, the indicators which reflect the various pressures on biodiversity continue to increase. For example, one-third of the sufficiently well-known species of animals and plants are currently classified as threatened (56,000 species).

### WHAT THESE RESULTS MEAN?

#### *Health implications*

Biodiversity loss has a variety of possible adverse consequences for humanity. Indeed, the two global megatrends, one in the state of biodiversity, i.e. altered biosphere, and the other in the prevalence of mucosal inflammatory diseases, may be closely linked.

Humans have evolved with the micro-organisms, which do not elicit defensive immune responses, but rather induce immunoregulatory circuits. A suddenly reduced abundance or diversity of these micro-organisms, previously ubiquitous, may have led to failures to regulate and restore appropriate immune and inflammatory responses.

*Inflammation* is a cardinal feature of asthma and allergic diseases, autoimmune diseases, and many forms of cancer, but more recently less tangible associations have been linked to these trends such as an increased incidence of obesity and depression associated with inflammatory markers. Thus far, the increase in the prevalence of inflammatory disorders is a phenomenon largely restricted to the developed world, while such

disorders are still uncommon among populations in non-affluent regions, i.e., those regions, which still have more traditional non-urban lifestyles.

Human commensals are no longer considered as passive bystanders or transient passengers, but increasingly as active and essential participants in the development and maintenance of barrier function and immunological tolerance. The indigenous flora may not only comprise bacteria and fungi, but also viruses and microscopic protozoans, although hardly any data on the latter are available.

### **Dysbiosis**

The reduced diversity and disturbed composition of the human microbiotas may have caused an imbalance of 'pro-inflammatory' and 'anti-inflammatory' microbes, i.e. dysbiosis and increased susceptibility of the host to inflammatory conditions. Collectively, sedentary lifestyle in affluent urban environments does not provide adequate microbial exposure to develop 'healthy' microbiota on the skin and mucosa. An indirect illustration of this concept is that faecal microbiota transplant has been successfully used to restore the microbiota balance in severe *Clostridium difficile* infections resistant to all other treatments.

### **Immune tolerance**

The concept of inducing tolerance and homeostasis may become a prime target for prevention and treatment strategies for many diseases of the modern time such as allergy, asthma, autoimmunity, obesity, some types of cancer as well as some mental and neurological disorders in which dysregulation of the immune system plays an essential role. We already know, that in allergy treatment,

inducing immune tolerance to allergens is characterized by establishment of a long-term clinical recovery. However, both the adaptive and innate immunity should be targeted to obtain long-term results.

### **CONCLUDING REMARKS**

Recently, the World Allergy Organisation Special Committee on Climate Change and Biodiversity published a position statement of the new biodiversity hypothesis.<sup>5</sup> It can be regarded as an extension of hygiene or "old friends" hypothesis and microbial deprivation or microbiota hypothesis. Population growth (urbanization) leads to loss of biodiversity (poor macrobiota/microbiota), poor human microbiota (dysbiosis), immune dysfunction (poor tolerance), inflammation and finally to clinical disease.

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