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OPINION

Hunt for the origin of allergy – comparing the Finnish and Russian Karelia

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Summary

The Finnish and Russian Karelia are adjacent areas in northern Europe, socio-economically distinct but geoclimatically similar. The *Karelia Allergy Study* was commenced in 1998 to characterize the allergy profiles in the two areas. Allergy prevalence had increased in Finland since the early 1960s, but the situation in Russia was unknown. The key finding was that allergic symptoms and diseases were systematically more common in Finnish children and adults than in their Russian counterparts. For example, in the early 2000s, hay fever in school children was almost non-existent in Russian Karelia, and only 2% were sensitized to birch pollen compared with 27% in Finnish Karelia. Adult birth cohorts showed that among those born in the 1940s, the sensitization to pollens and pets was at the same low level in both countries, but among younger generation born in the late 1970s, the difference was already manifold. Seropositivity to some pathogens, microbial content in house dust and drinking water seemed to confer allergy protection in Russia. In subsequent studies, it became apparent that on the Finnish side, healthy children had a more *biodiverse* living environment as well as greater diversity of certain bacterial classes on their skin than atopic children. Abundance of skin commensals, especially *Acinetobacter* (gammaproteobacteria), associated with anti-inflammatory gene expression in blood leucocytes. *In vivo* experiments with the mouse model demonstrated that intradermally applied A*cinetobacter* protected against atopic sensitization and lung inflammation. These observations support the notion that the epidemic of allergy and asthma results from reduced exposure to natural environments with rich microbiota, changed diet and sedentary lifestyle. Genetic studies have confirmed strong influence of lifestyle and environment. With our results from the Karelia study, a 10-year National Allergy Programme was started in 2008 to combat the epidemic in Finland.

Keywords allergy epidemic, allergy programme, biodiversity, immune tolerance, Karelia study, skin microbiome
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Why did we start?

In Finland, an active asthma programme was carried out between 1994 and 2004 to improve the treatment of asthma and to reduce the burden of disease in society [1]. During the period of this programme, both the mortality due to acute asthma and hospital admissions were reduced significantly. However, the increase in the prevalence of asthma and allergy, noticed in Finland since the early 1960s, continued [2]. Similar increase has been observed in other industrialized countries, and the asthma and allergy gap between developed and developing world has become evident [3].

These observations raised the question whether the increase in allergy and asthma prevalence in Finland is real or mainly explained by improved health care and better awareness of allergies. A window of opportunity for research opened up in the connection of the National FINRISK 1997 Study [4, 5]. In the spring 1998, additional sampling of data on allergy and asthma was carried out in North Karelia, Finland, and in the Pitkäranta region, Republic of Karelia in Russia. The province of North Karelia has around 165 000 inhabitants, while the Pitkäranta region has around 19 000. The first study subjects, randomly selected adults aged 25–54 years, filled in a detailed questionnaire on allergic symptoms and other factors based on the European Community Respiratory Health Survey (ECRHS). Skin prick tests (SPT) and blood sampling to analyse allergen-specific serum IgE levels were performed. The *Karelia Allergy Study* was commenced.

Same history but different post-war development

The border between the Finnish and Russian Karelia marks one of the sharpest boundaries in the standard of living and health in the world [6]. The adjacent areas are socio-economically distinct but geoclimatically similar. After the war, Finland has experienced major economic growth and rapid urbanization, which has created a striking socio-economic gap between the Finnish and Russian Karelia. The Republic of Karelia in Russia was almost completely closed to visitors during the Soviet era until 1991. The large area is sparsely inhabited by a population of about 640 000. The allergy study site, the Pitkäranta (Питкярнта) region, is located on the northern shore of the lake Ladoga, the largest lake in Europe (Fig. 1). Pitkäranta region was part of Finland until 1944. The original Finnish population was moved from the area at the end of the war, and the area was later populated by people from different parts of the Soviet Union. Nonetheless, the two current populations share partly the same ancestry. About 15% of the current population of the Karelian Republic are Finns or Karelians.

In 2012, around 19 000 people inhabited the Pitkäranta region, where the living conditions are simple and still largely resemble those in Finland half a century earlier. People have small houses in the country side with some cattle and domestic animals and produce much of their own food in small gardens. The household water is often taken from own well or spring. The pipe water has been largely surface water from the lake Ladoga, nowadays better chlorinated. Natural environment has been quite well preserved, although pulp mills and mining have had some negative environmental impact, in addition to providing jobs for local people. The region has only one town, called Pitkäranta (11 000 inhabitants), which has much less built environment compared with similar towns in Finland.

Comparison of these two areas, located about 200 km apart and called 'Finnish and Russian Karelia' below, has provided a natural laboratory to examine allergies in people having contrasting living conditions. The contrasts between East and West Germany, Estonia and Sweden as well as urban and rural Mongolia have provided somewhat comparable research opportunities [7–9]. There are limitations with such studies comparing just two populations with many possible confounding factors, but such comparisons are invaluable in revealing what needs to be explained, in raising questions about causality and in providing a point of reference for complementary, more focused studies. The *Karelia Allergy Study* has been developed in this context.

Adults appeared different

Self-reported allergic symptoms and asthma were much more common in the city of Joensuu and its surroundings in Finnish Karelia than in Pitkäranta in Russian Karelia. In Finnish Karelia, over 20% of adults (25–54 years) reported having hay fever, almost 25% had allergic eye symptoms (conjunctivitis), and over 25% had atopic eczema. A little more than 5% reported physician-diagnosed asthma. In Russian Karelia, the respective prevalences were less than 5% for hay fever and allergic eye symptoms, slightly over 10% for atopic eczema and 2% for physician-diagnosed asthma [4].

The more objective measures, skin prick tests (SPT) for atopic, IgE-associated sensitization to common allergens, confirmed the observed differences between the areas. Positive SPT reactions showing sensitization to pollen allergens (birch and timothy grass) as well as to cat were much more common on the Finnish side. The percentage of those having at least one positive SPT reaction was nearly 35% in Finnish Karelia compared with 20% in Russia. Some likely explanations of these disparities were provided by the differences in seropositivity to various pathogens such as *Helicobacter pylori* (bacteria), *Aggregatibacter actnomycetemcomitans* (bacteria), *Toxoplasma gondii* (single cell parasite) *and Herpes simplex* (virus), suggesting that an active immune process against pathogens may improve the immune tolerance to harmless, environmental bioparticles such as pollens or animal danders [10]. This has been observed in other populations as well [11, 12].

Smoking is a major risk factor for BHR, but atopy only in Finnish Karelia

A methacholine challenge test to measure bronchial hyperresponsiveness (BHR) was performed for 581 Finns (27% smokers) and 307 Russians (42% smokers) [13].

Fig. 1. The study areas. North Karelia in Finland and Pitkäranta region in the Republic of Karelia in Russia. The dashed lines are Finnish borders before 1944.

The prevalences of BHR (22% vs. 19%) and sputum eosinophilia (14% vs. 13%) were the same among the Finnish and the Russian adults, but the risk factors were partly different. Smoking was the most significant risk factor for BHR in both areas, but in Finland, also atopic allergy was a major risk factor for BHR.

. . .and children even more so

Research findings on adults raised an interest to assess whether the differences between the countries existed already among children. In 2003, around 500 children aged 7–15 years and their mothers from both regions were invited to take part in a survey analysing asthma and allergy prevalences and their environmental and genetic causes. Families filled in a questionnaire and, children and mothers participated in a health check-up including SPT, blood sampling and DNA collection. Dust samples from homes were collected. In addition, the study team took water samples from all the schools attended by the participating children.

The difference in allergic conditions and sensitization to common allergens was even more pronounced among the children than in adults (Fig. 2) [14]. Physician-diagnosed asthma was 5.5-fold more frequent in Finland than in Russia (8.8% vs. 1.6%). For hay fever, the difference was 14-fold and for eczema fivefold. Asthma, rhinitis and eczema in Russian Karelia were not only rare but, to a large extent, had no sIgE component [15]. Seventy-seven per cent of the Finnish children and 43% of the Russian children with asthma were sIgE positive (cut-off > 0.35 kU/L). The respective figures for hay fever were 94% and 67%, and for eczema 68% and 41%. This discrepancy was similar but of lower magnitude among the mothers. Almost 45% of the Finnish children had at least one positive SPT reaction compared to 16% among the Russian children. Among mothers, the respective percentages were 36% and 18%.

Among the Finnish school children, atopic sensitization was inversely related to the amount of microbial components in house dust [16]. Atopy was most readily observed among those who had the smallest index for chemical microbial markers, indicating microbiologically poor dust in their homes. Comparing the two regions, the microbial cell count of the drinking water in Russian Karelia was almost ten times higher than in Finnish Karelia. Multivariate regression analysis to

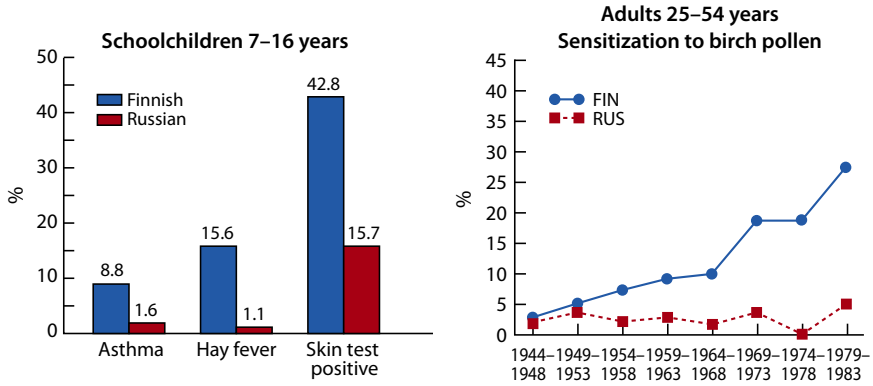

Fig. 2. Allergic conditions and sensitization to allergens were much more common in Finnish compared with Russian schoolchildren (left panel) [14]. Generational increase in positive allergen-specific IgE levels to birch pollen in the Finnish but not in the Russian Karelia (right panel) [24]. Among older generations, born in the 1940s, the prevalences were at the same low level in Finnish vs. Russian Karelia.

identify factors associated with the occurrence of atopy revealed that microbe-rich drinking water was strongly associated with the reduced risk for atopy in Russia [17].

It was noteworthy that seropositivity to *Herpes simplex* virus was associated with the lower prevalence of allergic sensitization in the Finnish environment with relatively low overall microbial burden, but not in the Russian environment with rich microbial burden [18].

We studied one parasitic nematode worm, *Ascaris lumbricoides,* which is not endemic but still quite prevalent in Russian Karelia and virtually non-existent in Finland. Based on the IgE responses to *Ascaris,* it seemed that this parasite did not confer protection against atopy in Russia and did not explain the observed disparity in the prevalence of atopy between Finnish and Russian Karelia [19].

What is the role of house dust mite?

While the contrast in the sensitization to pollens and pets was remarkable between Finnish and Russian school children (e.g. 27% vs. 2% positive SPT to birch pollen), there was no difference in sensitization rate against house dust mite (HDM) (*Dermatophagoides pteronyssinus*). Around 9% of children in both areas showed positive SPT [14]. However, there was a clear difference in the percentage of those who only responded to HDM and not to any other allergens: 5% in Russia vs. 1% in Finland. It appeared that HDM-monosensitized children were mostly free of symptoms, while the polysensitized children had a clear risk for atopic disease. Thus, HDM monosensitization was not associated with clinical disease but was a marker of exposure only [20]. This has been confirmed recently for adults [21]. The mite exposure was much greater in Russia where the microscopic analysis of house dust samples showed high counts (mean 125 mites/g dust), whereas the dust mites were virtually absent in the Finnish samples.

House dust mites are ectodermal parasites, and it might be biologically meaningful to have an immunological response to mites in a mite-rich environment. Some mites, such as *Blomia tropicalis*, may even invade the skin. Only when this response escalates to IgE formation against other bioparticles such as pollens and animal allergens, the individual carries a risk of clinical allergic disease. The evidence from Russian Karelia does not support the concept that increased exposure to HDM in early life is associated with the increased risk of asthma and related symptoms later in life.

The hallmark paper on mites was published in 1964 by Voorhorst and co-workers [22]. They concluded that 'now it seems that we have found Mr X, and everything indicates that he may be the criminal'. Based on the Karelia observations, our verdict is as follows: have attended the place of crime but not guilty of assault [23]. In polysensitized subjects, mite exposure may evidently contribute to symptoms, but in Russian Karelia, in a microbe- and mite-rich environment, mites are mostly innocent bystanders.

The younger generation is more allergic in Finland but not in Russia

In 2007, 10 years after the first cross-sectional survey study of 25- to 54-year-old adult population, a second survey among adults of the same age group was performed. It was anticipated that the difference in atopy between the two areas might have decreased as Pitkäranta region has been more open to western influence. But this was not the case. The prevalence of positive allergen-specific IgE levels to common allergens in Finnish Karelia had increased while there was no change in Russia [24]. Analyses of these data by birth cohort showed that in Finland, the increase in prevalence

occurred in younger generations (Fig. 2). Among older generations, born in the 1940s, the prevalence was at the same low level both in Finnish and in Russian Karelia, but among those born in the late 1970s, the difference in prevalence was manifold.

Genetics did not explain the contrast in allergy

In Finnish and Russian adult women, we found an interaction between the genetic effects of certain genes (*CD14* and *CC16*) and the environment. But, surprisingly, the Finnish environment, compared to the Russian one, appeared to have an effect on allergy risk via opposite alleles. Finnish children had a different genetic profile associated with asthma and allergy than Russian children. Several innate immunity genes that were associated with asthma-related phenotypes in Russian Karelian children tended to have the opposite effect in Finnish Karelian children. In summary, the studied individual genetic background did not determine whether a subject will become sensitized or develop clinical allergy. It appeared to depend more on environmental factors [25, 26].

Recently, we have shown that some maternal genetic variants in IL-4/IL-13 pathway genes influence IgE levels in school children and that these effects are independent of children's own genetic effects. The maternal effects differed between the Finnish and Russian environments. Again, the result indicated a strong lifestyle and environmental influence in the risk of sensitization to common allergens [27].

. . . but poor biodiversity did

Microbial diversity and immune tolerance

The bacterial composition of house dust samples (20 randomly selected dust samples from Finnish and Russian households) was examined by 16S rRNA gene sequencing obtained from the dust contained DNA [28]. Overall, these analyses revealed 94 different genera of bacteria from the dust samples. The majority (67%) of the bacterial sequences from the low-allergy Russian Karelia represented Gram-positive bacteria (Firmicutes and Actinobacteria), predominantly Staphylococcaceae and Corynebacteriaceae. Russian Karelian dust showed up to 20-fold higher content of muramic acid (marker of Gram-positive bacteria) and a sevenfold greater number of animal-associated species, whereas in Finnish Karelian dust, Gram-negative taxa predominated (mainly Proteobacteria). The study revealed major disparities between the Finnish and Russian house dusts both in microbial quantity and in *diversity*, which was much greater in Russia.

To complement the above studies, we compared urban home dust and barn dust from the Helsinki area [29]. The respective bacterial communities turned out to be highly contrasting. For example, in the urban dust, cultured on plates, Gram-positive bacteria were mostly Bacilli, while those in the barn dust were mainly Actinobacteria. The latter have been found to predominate in soil microbiota [30] and to represent also one of the most abundant groups of freshwater bacteria [31]. Seven different genera of Gram-negative bacteria grew in the barn dust, which were virtually lacking in the urban dust. Bacterial *diversity* was remarkably higher in the barn dust. The rank-abundance distribution curves (Fig. 3) and the evenness measures indicated a more even distribution of bacterial genera in the barn dust, in which no taxa reached dominance, in contrast to *Corynebacterium* and *Streptococcus* in the urban house dust. Diverse barn dust contained numerous genera (about 30) at low prevalence (1–5% of the total). Intranasal administration of house dust to mice elicited pulmonary eosinophilia, while barn dust elicited increase in neutrophils and lymphocytes. Stimulation of human dendritic cells with house dust or barn dust had a contrasting effect on naïve T cells, the latter dust directing the response towards Th1-dominated immune response.

We concluded that urban dust, containing mainly bacterial debris of human commensal species, may stimulate pattern recognition receptors in a suboptimal way to develop and maintain immune tolerance. To put it simply: *urban people are repeatedly exposed to their own microbiota, which is not enriched by microbes from variable natural environments*.

Based on these results, it was not surprising that exposure to house dust rich in microbes in Russian

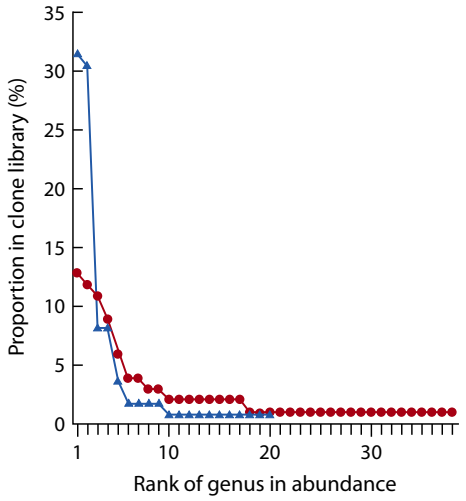

Fig. 3. Rank-abundance curves of the bacterial genera in the 16S rRNA gene clone libraries from DNA of urban house dust (▲) and barn dust (●). The figure shows the percentages of prevalence (rank 1 for the most abundant genus) [29, with courtesy of Int Arch Allergy Immunol].

Karelia was associated with tolerance and strongly reduced risk of atopic manifestations, when many of the confounding factors were taken into account [16]. Similar observations were made by a German group. They showed that children growing up in farms, and exposed to wider range of dust microbes than the reference group, obtained protection against asthma [32].

The differences in dust microbiota between Russian and Finnish households, and between urban and rural Finnish homes, are, however, only one of contrasts in lifestyle and environment, which characterize the transition from a traditional rural to a modern urban way of life. For example, a consistent finding from the Alpine regions, and from some farming studies elsewhere, has been a reduced risk of allergy in families consuming unpasteurized milk. Whether this protective effect is mediated by the microbial content or rather in the whey fraction of unprocessed cow's milk is debated [33]. In the Russian Karelia, consumption of unpasteurized milk used to be common, but nowadays, processed milk is increasingly used. In Finland, very few people have used unprocessed milk during the last 20–30 years.

Environmental biodiversity and immune tolerance

The biodiversity issue was even more in focus when the study subjects in the 2003 survey were examined again in 2010–2011 in Finland, at which point they were adolescents (14–18 years old). Blood and skin swab samples were obtained, the latter to characterize the composition of the microbiota. Additionally, land use in the surrounding of their homes was described, and the plant species composition in the yards was identified. Peripheral blood mononuclear cells (PBMCs) were extracted from blood samples, and cytokine expression was measured. Microbial DNA from the skin swab samples was analysed, and diversity of the skin microbiota thereby assessed. Although the sample size was relatively small (n = 118), it was found that healthy children in Finland had a more *biodiverse* living environment with more green space, natural areas and more flowering plant species in the yard as well as more diverse assemblage of microbiota on their skin compared with atopic children (Fig. 4). Healthy children had a strong association between the abundance of *Acinetobacter* on the skin and the expression of the anti-inflammatory cytokine IL-10, while there was no such relationship in atopic children [34].

We further analysed four study cohorts from Finland and Estonia (n = 1012) consisting of children aged 0.5–20 years. The cover of forest and agricultural land within 2–5 km from the home, and especially the home at the time of birth, was inversely associated with the sensitization to inhalant allergens [35]. Land-use

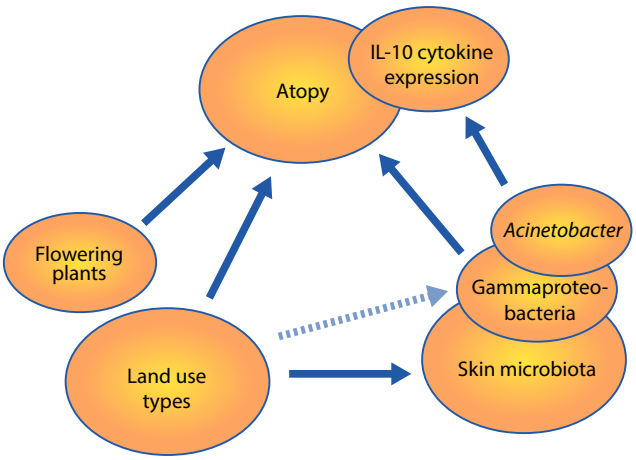

Fig. 4. Summary graph of the associations among environmental biodiversity, skin microbiota, IL-10 expression of peripheral blood mononuclear cells and atopy. The solid arrows refer to significant associations, and the dashed-line arrow indicates a less significant effect [34, with courtesy of Proc Natl Acad Sci USA].

pattern explained 20% of the variation in the relative abundance of Proteobacteria on the skin of healthy individuals, supporting the hypothesis of a strong environmental effect on the commensal microbiota. Our analysis also suggested a protective effect for farm milk consumed around 1 year of age, but this was confounded by the fact that farm milk consumption was limited to children living in areas with high cover of green space (> 60%).

Skin commensals tune allergen immune responses

To reiterate, we found that the relative abundance of *Acinetobacter* in the skin microbiota of healthy teenagers was associated with the IL-10 expression in blood PBMCs. This prompted us to study the role of skin microbiota further [36]. The abundance of allergy-protective Gammaproteobacteria on the skin was associated more generally with the anti-inflammatory gene expression in human PBMCs. A*cinetobacter* induced anti-inflammatory and TH1-type gene expression in dendritic cells and keratinocytes *in vitro*. When these bacteria were intradermally applied in the mouse model, they protected against atopic sensitization and lung inflammation. We concluded that immune tolerance is developed as a fine-tuned balance between different immunocompetent T cells (Th1, Th2, Th17, Tregs) (Fig. 5).

A skin flora dominated by *Acinetobacter* is probably just one indicator of a lifestyle and environment which has more general effects on the development of allergic sensitization. Nevertheless, these experiments supported previous observations showing that abundant and diverse skin microbiota contributes to immune homeostasis and protects from unnecessary responses to

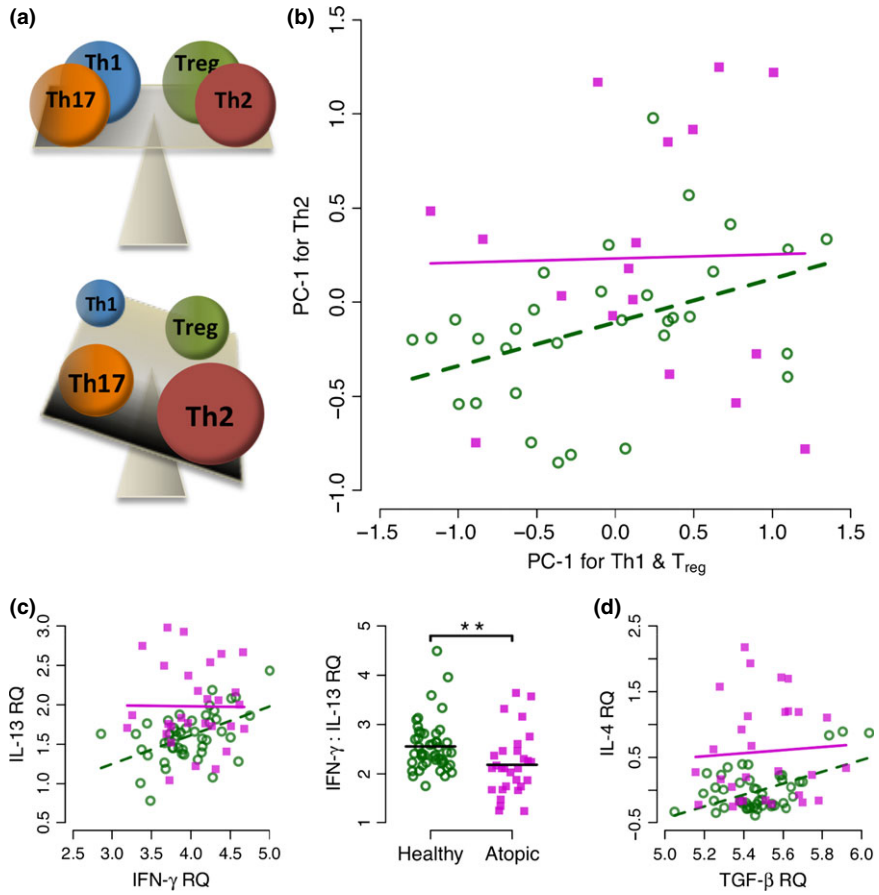

Fig. 5. (a) Adaptive immune responses in healthy individuals are balanced, but Th2 dominates in atopy. (b) Th2 correlated ($P = 0.021$) with Th1/Treg immune responses, (c) IFN-γ correlated with IL-13 and was expressed at relatively higher level (**$P < 0.01$), and (d) IL-4 correlated with TGF-β, in the healthy (open symbols), but not in the atopic (solid symbols) individuals [36, with courtesy of J Allergy Clin Immunol].

harmless bioparticles. The results also supported the general idea that a biologically rich and diverse natural environment enriches the human commensal microbiota and prevents from inappropriate inflammatory responses [37].

Is it the chemicals, after all?

Previous studies on environmental chemicals and atopy have produced inconsistent results. There is some evidence that exposure to persistent organic pollutants (POPs) could favour atopic disposition, but also evidence that POPs could even offer protection against atopic diseases. Methodological inconsistencies may explain some of the variation in the results. We studied 25 atopic and 25 non-atopic school-aged children and their mothers in Finland and in Russia, altogether 200 individuals, and measured 11 common environmental chemicals in blood samples (Koskinen *et al.*, unpublished data). Overall chemical concentrations were higher in Russia than in Finland except for a brominated flame retardant (BDE47), not supporting the idea that environmental chemicals lead to atopy.

The usage of pesticides, including DDT, and PCBs has been more recent in Russia than in Finland, demonstrated by higher concentration of DDT in Russian serum samples. Other explanations for higher concentrations of pesticides in Russian samples are contaminated soils and poorly maintained stocks of obsolete pesticides. In any case, these studies suggested that exposure to environmental chemicals is not a major explanatory factor of the allergy epidemic.

Latest news from Karelia

In 2012, a follow-up survey of the teenagers and young people was carried out also in the Russian Karelia to assess allergies, to collect samples (skin and nasal swabs, blood) and to make the same environmental assessments as in Finland in 2010/2011. There were two main questions. What has happened to the atopy gap between Finland and Russia in 10 years? Secondly, what are the environmental influences on the immune tolerance in Russia?

The preliminary results indicate that the allergy gap between Finnish and Russian 14–20-year-old people

has remained the same during the 10-year period (Paalanen *et al*., unpublished data). This result confirms that the allergen immune responses are mostly determined before the school age, as is known from previous studies [38], and the changes are much smaller after that.

Another Finnish group has also made comparisons between Finland and Russian Karelia, exploring first the cross-border differences in type I diabetes [39] and proceeding to allergy and autoimmune conditions. They conclusions accord with ours: environmental factors have greatly contributed to the increasing prevalence of immune-mediated disorders [40].

Change in thinking and an action plan

The Karelia allergy study has been instrumental in the development of a new hypothesis of the causes of the so-called allergy epidemic in developed countries. Changes in lifestyle, nutrition and environment along with rapid urbanization have all contributed to changes in human microbiome, which mediates the cross-talk between man and the environment. The Finnish Karelian population seems to have lost contact with some of the environmental factors that are fundamental for the development of immune tolerance, factors that still largely prevail in Russian Karelia.

The Karelian results suggest that contact with a diverse natural environment with abundant bacteria (saprophytes) and other micro-organisms may protect people from becoming sensitized to allergens, by building up strong innate immunity and tolerance. The biodiversity hypothesis is changing our thinking and enlarging the focus from allergies to other chronic inflammatory conditions, including even cancer, obesity and Alzheimer's disease (Fig. 6). These disorders, associated with inflammation, are on the increase all over the world. In allergies, the most rapid changes are now taking place in the rapidly urbanizing countries such as China and India. In Finland, the cross-border Karelian results stimulated a national act, the Finnish Allergy Programme 2008–2018 [41, 42]. The first results have been encouraging, and a new track has been opened [43].

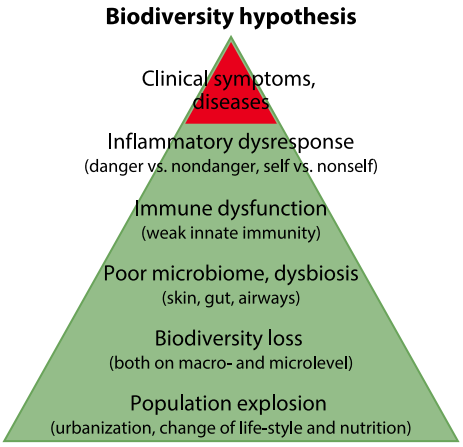

Fig. 6. The biodiversity hypothesis linking environment and lifestyle changes to immune dysfunction and human disease [37,53].

Where are we now?

We believe that the recent allergy epidemic is most likely caused by the loss of protective and immune balancing factors due to modern, urban life. Farm living gives a strong protection against childhood asthma and allergy [44], but it is noteworthy that also in inner-city environments, children with the highest exposure to diverse allergens and bacteria during their first year of life were least likely to have recurrent wheeze and allergic sensitization [45]. These findings suggest that concomitant exposure to high levels of certain allergens and bacteria in early life is beneficial. New risk factors and controversies (vitamin D supplementation, chemicals, pollutants, allergens etc.) will emerge, but it seems unlikely that they would be major causes of the allergy epidemic. The key is immune tolerance and its determinants.

Life on earth originated from sea and soil, and all biological life is interconnected. Biodiversity is defined as the variety of life on earth. It includes the genes of living things as well as all species they comprise and the ecosystems they inhabit [46]. In 1850, the world population was somewhere between 630 and 930 million, 160 years later over 7,2 billion. The exponential population growth and rapidly escalating urbanization have led to a serious loss of biodiversity. Ecologists are speaking of the sixth mass extinction, caused by man, as the rate of species loss is 1000 times higher than the long-term background rate. Habitat destruction, pollution and climate change contribute to deteriorating living conditions in many parts of the planet. Habitat destruction and declining numbers of vertebrates are especially alarming in the tropics [47].

Loss of environmental biodiversity leads to reduced human microbiota (dysbiosis), immune dysfunction (poor tolerance), inappropriate inflammatory responses and finally symptoms and disease. The interplay of environmental metagenome, human microbial genome and human genome determines health and disease. Everything we eat, drink, touch and breathe modulates the microbiome and keeps immune processes alert. Maybe the more urbanized Finns have been disconnected from the soil microbiota [48] earlier than their Russian counterparts (Fig. 7).

Immune tolerance is an active process throughout life, although the early events are most important [49]. Build-

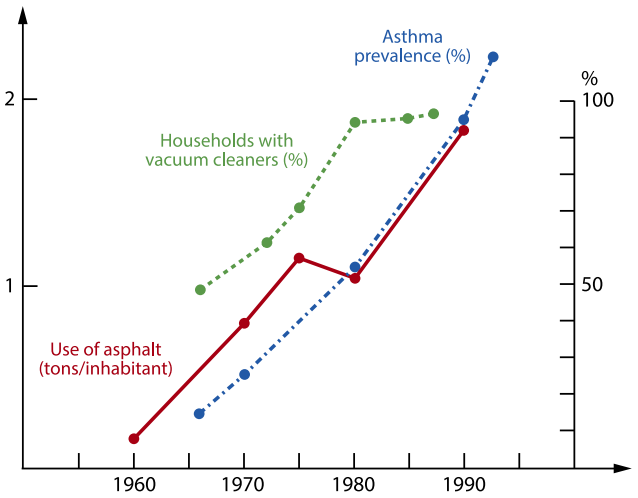

Fig. 7. Use of asphalt (tons per inhabitant per year) from 1960 through 1990, households with vacuum cleaners and occurrence of diagnosed asthma among military conscripts from 1966 through 2000 in Finland [2, 48, modified]. Vacuuming reduce dust microbes more than sweeping [28].

ing up safe connections to beneficial and balancing saprophytes and commensals is prerequisite to better immune health [50, 51]. These premises are included in the prevention practice of the Finnish Allergy Programme. For symptomatic patients, immunotherapy is increasingly used, not only for allergy but also for other immunological/inflammatory conditions, even for some forms of cancer. Combining the activation of both the adaptive and innate immune functions with new kinds of therapeutic preparations may be a step forward. Birch pollen-enriched honey gave excellent therapeutic results in allergic patients [52]. The honey preparation has not only the desensitizing birch pollen but also 1.2 billion bacteria per ml.

We conclude that the epidemics of chronic inflammatory diseases, including allergy and asthma, are largely the result of reduced exposure to natural environments, changed diet and sedentary lifestyle [53, 54]. We need to change our thinking and start to plan actions to safely restore our connections to nature. This means that environmental protection, urban planning and food production, storage and delivery, as important determinants of public health, should have higher priority in the political agenda. It is critical that individuals realize how their choices in everyday life make a difference also in terms of allergy risk and management.

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Conflict of interest

The authors declare no conflict of interest.

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