

## Podcast interview – Jenni Lehtimäki and Stefan Reber

**PNAS:** Welcome to Science Sessions. I'm Paul Gabrielsen. More than half of the world's population now lives in urban areas. Researchers have noticed a difference, though, in the health of urban residents compared with rural residents. By some accounts, rural residents report fewer cases of allergies, asthma, and psychiatric disorders than urban residents. Why the difference? Allergies and asthma are disease of hyperactive immune activation – the immune system overreacts to environmental triggers. In stress-associated mental disorders as well, researchers have noticed an accompanying overreactive immune system and chronic inflammation.

Many people living in largely animal-free urban environments are generally not exposed to the same suite of microbes as people living on farms, in large families, or with multiple pets. The microbes typically found in rural environments are more diverse than those in urban environments, and one hypothesis states that our immune systems need to be challenged by natural environment microbes to develop properly. Without that exposure, the hypothesis holds, our systems are less able to reign in inflammation.

The hypothesis is called the 'biodiversity hypothesis,' and was explored in two recent studies in PNAS. In the first, Jenni Lehtimäki of the University of Helsinki sought to understand how urban and rural lifestyles affected the development of allergies. Lehtimäki herself grew up in a rural environment.

**Lehtimäki:** I don't have any allergies. But when I think of my history, I had all sorts of protective factors which we now know are protective. I had siblings, and they are older than me, so I was exposed to older siblings. I grew up in a rural area. For example, my school was between two farms, so both sides of the school, there was cows.

**PNAS:** Many factors can affect the development of allergies in humans, she says, so instead she and her colleagues looked at dogs. Specifically, dogs kept as pets.

**Lehtimäki:** Allergic diseases had increased, not only in humans but also in dogs. So we realized that dogs also shared the living environment with humans, and earlier studies had shown that dogs also somewhat share their microbiota with their owners. So therefore we thought that pet dogs are the perfect real-life model animal to understand allergies as their life is more simple and shorter than that of humans, while they also share the living environment and diseases with humans.

**PNAS:** They studied 169 Labradors and Finnish lapphunds from various home lifestyles. After swabbing the dogs' skin to sample the skin microbiome, the researchers also asked the owners to complete a questionnaire on the dog's living environment, lifestyle, and allergic symptoms.

**Lehtimäki:** Dogs which were living in a rural environment in a large human family, they're least likely to develop allergies, while the dogs which were living in urban areas with a single human, without animal contacts were most likely to develop allergies. Also the skin microbiota of dogs living in different environments or having dissimilar lifestyles differ. We show that exposure to microbes through lifestyle and living environment, skin microbiota

and risk of allergy were all interrelated, at least in the pet dogs. We think our results also apply to humans.

**PNAS:** The factors that lead to allergies are complex, and this study was not able to unravel them to the point that the authors could say definitively what people should do to prevent allergies.

**Lehtimäki:** I exercise outdoors as much as I can and I also have a horse riding class every week. I dream to have a dog but I don't have it yet. These are things I try to be doing. But it's pretty hard in an urban environment to truly have this sort of large exposure to environmental microbes.

**PNAS:** In another recent PNAS study, Stefan Reber of Ulm University and colleagues sought to understand why psychiatric disorders occur at higher rates in urban versus rural environments. Reber says previous work showed that people with depression or people carrying risk factors for depression exhibited an elevated immune response to stress. According to some studies, Reber says, an overreactive immune response may be associated with the development of depressive episodes or a state of depression. He and his colleagues explored the psychological aspect of the biodiversity hypothesis. He also grew up in a rural environment.

**Reber:** I grew up in a beautiful small village in the countryside, but unfortunately had not regular contact to farm animals or furred pets.

**PNAS:** The study included 20 rural-raised men who grew up around farm animals and 20 urban-raised men who grew up without pets. Both groups underwent a standard social stress test, including a mock public speech. Reber explains the test's effects.

**Reber:** We employed the Trier social stress test, which is abbreviated as TSST. It was developed for inducing a moderate psychosocial stress response in an experimental laboratory setting. The TSST is also well known to activate the immune system.

**PNAS:** The researchers monitored the participants' physiological signs of stress – activation of the sympathetic nervous system, or SNS, activation of the hypothalamic–pituitary–adrenal, or HPA axis, and levels of the stress hormone cortisol. They also measured signals of immune system activation.

Rural men reported feeling more stress from the test than urban men. But urban men experienced a high and sustained immune response.

**Reber:** Such a disparity only exists between perceived stress levels and stress-induced immune activation. It is not existing between perceived stress and physiological stress response these participants showed. When you look at the HPA axis, at the baseline cortisol levels, and also at sympathetic nervous system activity, then you can see that an increased

feeling of stress in the rural participants is indeed linked to an increased basal cortisol level and also to a slightly prolonged TSST-induced SNS activation. Although the urban participants did not feel extremely challenged by the TSST situation, their body unconsciously launched a pronounced and very long-lasting immune activation. And my colleague and co-author Prof. Lowry compared this with a sleeping giant that they are completely unaware of.

**PNAS:** It's a sleeping giant because prolonged immune response and inflammation can increase risk for physical and mental disorders. However, Reber cautions, the study doesn't draw a definitive causal link between growing up with animals and an immune response to stress.

**Reber:** But considering the aforementioned studies from colleagues working in the allergy field a substantial role of pets and/or farm animals as a source of biodiversity is very likely, also in the context of stress-induced mental disorders.

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