

People who preserve 'immune resilience' live longer and resist infections, study finds

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Sunil Ahuja, Muthu Manoharan et al. describe immune resilience to explain why some people, regardless of age, have intact immune systems and reduced inflammation while others do not. The blue-clad spheres are T-cells. The lower sphere is COVID-19 featuring its characteristic red spike proteins. Credit: The University of Texas Health Science Center at San Antonio

Researchers from The University of Texas Health Science Center at San

Antonio, working with collaborators in five countries, have revealed that the capacity to resist or recover from infections and other sources of inflammatory stress—called "immune resilience"—differs widely among individuals. The researchers developed a unique set of metrics to quantify the level of immune resilience. This will aid in decisions for health care and help researchers understand differences in life span and health outcomes in persons of similar ages. These findings were published in *Nature Communications*.

Although age plays an important role in the body's response to infectious and other inflammatory stressors, some persons preserve and/or restore optimal immune [resilience](#) regardless of age, noted first and senior author Sunil K. Ahuja, MD, professor at UT Health Science Center San Antonio with a specialty in [infectious diseases](#). He is director of the Veterans Administration (VA) Center for Personalized Medicine, a national center within the South Texas Veterans Health Care System.

"Immune resilience is the capacity to maintain good immune function, called immunocompetence, and minimize inflammation while experiencing inflammatory stressors," said Weijing He, MD, co-author and senior research scientist at the VA Center for Personalized Medicine and Foundation for Advancing Veterans' Health Research. "We found that during aging and when experiencing inflammatory stress, some persons resist degradation of immune resilience."

The laboratory tests developed to assess levels of immune resilience were evaluated in nearly 50,000 persons of differing ages and types of challenges to their immune systems. This evaluation demonstrated that individuals with optimal levels of immune resilience were more likely to:

- Live longer.
- Resist HIV and influenza infections.
- Resist AIDS.

- Resist recurrence of skin cancer after kidney transplant.
- Survive COVID-19 infection.
- Survive sepsis.

The researchers measured immune resilience in two ways:

- By measuring the balance between CD8⁺ and CD4⁺ T-cells, which are types of white blood cells. T-cells fight infections, but an imbalance in their levels occurs in many infectious and autoimmune diseases. The balance between CD8⁺ and CD4⁺ T-cells, divided into four distinct categories called immune health grades, was measured in varied infection cohorts and across the age spectrum.
- By measuring the expression levels of genes linked with immunocompetence and a greater chance of survival versus those linked with inflammation and a higher risk of death. The gene expression markers signifying high immunocompetence and low inflammation were identified with the immune health grade tracking optimal immune resilience.

"Many people think of inflammation alone when considering disease outcomes," explained co-author Grace C. Lee, PharmD, Ph.D., research investigator at the VA Center for Personalized Medicine and assistant professor at The University of Texas at Austin College of Pharmacy. "However, the concept of immune resilience captures levels of immunocompetence and inflammation together."

'A step forward'

The study introduces the novel concept of immune resilience, which looks at the balance between immunocompetence and inflammation as a critical contributor to [health outcomes](#), regardless of age.

"This is an advantage and a step forward because by looking beyond inflammation, we may uncover new prevention and treatment strategies for chronic diseases such as cardiovascular disease, COVID-19, HIV/AIDS and cancers," Lee said.

Framingham analysis

Muthu Saravanan Manoharan, MS, co-author and senior research scientist at the VA Center for Personalized Medicine and UT Health Science Center San Antonio, noted that the study team divided participants from the Framingham Heart Study into four groups based on the gene expression markers of immune resilience.

"Participants with optimal immune resilience, defined by gene expression markers signifying high immunocompetence and low inflammation, lived longer after controlling for the effects of age and sex," Manoharan said. "Participants with metrics signifying low immunocompetence-high inflammation died sooner, whereas those with a combination of high immunocompetence-high inflammation, or low immunocompetence-low inflammation, had life spans that fell in between."

Influenza

The study team also examined gene expression markers of immune resilience in a population of healthy college students and individuals in the community, all under age 50, who had blood drawn before the influenza season started. On the day of the first symptoms, most participants, including those with optimal immune resilience before the flu-like illness, had gene expression profiles indicating low immunocompetence and high inflammation, which is noted in persons with shorter life spans.

Many people restored their initial level of immune resilience during recovery; however, even some of those who had optimal immune resilience before influenza infection failed to do so. "Six months after their flu, some people continued to have gene expression signatures of poor immune health," noted Nathan Harper, MS, co-author and senior biostatistician at the VA Center for Personalized Medicine and Foundation for Advancing Veterans' Health Research. "This is rather striking, because it means that inflammatory stressors like influenza can degrade a vulnerable person's immune health long term."

Sex workers

The study examined female sex workers from Kenya. During a long-term study, the immune health grades of those with unprotected sex decreased. "Most of the HIV acquisition occurred in women who had lower immune health grades," said Lyle R. McKinnon, Ph.D., co-author and associate professor in the Max Rady College of Medicine, Department of Medical Microbiology and Infectious Diseases, at the University of Manitoba, Canada.

"With guidance and tools for safe sex practices, women with a lower frequency of unprotected sex over a 10-year time frame had restored optimal immune resilience, suggesting that removal of an immunological stressor could lead to the restoration of a healthier immune status."

HIV-AIDS

In one of the cohorts, the authors observed a rare ability to maintain a high level of immunocompetence with a low level of inflammation despite chronic inflammatory stress, termed elite immune health status. "Interestingly, we found that some younger adults preserved optimal immune resilience markers despite HIV infection," said Jason F.

Okulicz, MD, U.S. Air Force infectious disease physician and senior member of the study team. "The preservation of these markers associated with resistance to developing AIDS and a low level of HIV in the blood.

Remarkably, we found that after starting antiviral therapy early, some HIV-positive persons manifested markers of optimal immune resilience typically observed in younger adults without HIV infection."

COVID-19

The association between immune resilience and the response to infection was noted during other infections. About 80% of individuals had poor immune health grades at presentation with acute COVID-19, and their immune grade predicted mortality, regardless of age.

"Even among patients with serious community-acquired pneumonia and sepsis, those who had higher levels of gene expression markers of immune resilience at admission to the intensive care unit were more likely to survive," noted co-author Justin Meunier, BS, research scientist at the VA Center for Personalized Medicine.

Kidney transplant recipients

Immune resilience was also measured in kidney transplant recipients, who have a 100-fold excess risk of developing skin cancer. Each of the participants had developed this cancer once after transplant. "We explored the risk of getting a second cancer, dependent on immune health grades at the time each participant had the first cancer," said Matthew J. Bottomley, MD, DPhil, academic clinical lecturer in the Nuffield Department of Surgical Sciences, University of Oxford. "We found that, if someone had optimal immune resilience at the time of the

first cancer, they resisted getting their second cancer."

In collaboration with investigators from Sardinia, the authors examined blood immune cell profiles of nearly 4,000 otherwise healthy individuals. "We found that irrespective of age, persons with poor immune resilience had immune cell profiles reflecting increased immune activation," noted co-author Edoardo Fiorillo, Ph.D., of the Institute for Genetic and Biomedical Research, National Council of Research, Lanusei, Italy. "Interestingly, we observed that nonhuman primates with poor immune resilience also manifested similar immune cell profiles."

Females show greater immune resilience

One consistent finding throughout the populations studied was that age was not the single determinant factor in a person's response to inflammatory stress. Some younger persons with poor immune resilience had the same signatures and immune health grades commonly seen in older persons. This finding suggests that the ability to restore and maintain immunocompetence at younger ages may be linked to life span.

Another factor noted across the populations and species was that higher levels of optimal immune resilience were observed more often in females than males. Genetic studies in humans and evaluation of mice with a genetic basis to have lower immune resilience suggest that immune resilience may be calibrated by variations in genes. Notably, mice with lower immune resilience were most susceptible to severe Ebola infection.

Understanding risks

Public health ramifications of immune checkups could be significant, Ahuja said. He noted that assessment of immune health grades estimated

by CD8⁺ and CD4⁺ counts is a simple way to monitor immune resilience.

These assessments have utility for understanding who might be at greater risk for developing diseases that affect the immune system, how individuals are responding to treatment, and whether, as well as to what extent, they will recover.

More information: Sunil Ahuja, Immune resilience despite inflammatory stress promotes longevity and favorable health outcomes including resistance to infection, *Nature Communications* (2023). DOI: [10.1038/s41467-023-38238-6](https://doi.org/10.1038/s41467-023-38238-6).

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