

# **A way of life that keeps cells young in one region of Costa Rica**

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Epidemiologist David Rehkopf and a longtime collaborator have pioneered research into why and how people in certain regions of the world—including Nicoya, Costa Rica—live especially long and healthy lives. Credit: Stanford

University

In Nicoya, Costa Rica, where average incomes are among the nation's lowest, the average life span is 85—among the world's highest. By comparison, a person in the United States can reasonably expect to live to just 77, according to federal census data.

So why is it that the people of Nicoya outlive so many others?

For a long time, scientists and demographers pointed to a handful of qualities seen in regions around the globe like Nicoya with extreme longevity: meaningful and plentiful social connections, consumption of unprocessed foods and living in communities in which walking is the main form of transport. It's a sensible observation, but it's short on scientific detail, said David Rehkopf, ScD, associate professor of epidemiology and [population health](#) and of medicine at the Stanford School of Medicine.

Rehkopf is uncovering those details. In the past 15-plus years, his studies in Nicoya have identified social factors, an immune system trait and chromosomal features—telomere length and [methylation patterns](#)—that correlate with longevity there. Now, he's studying other regions of longevity in Greece and Italy and has found the same correlations.

"Our questions are, "Can we figure out the social and biological reasons why people live so long in this area?" said Rehkopf. (Maybe it's Nicoya's lack of grinding desk jobs that keeps their telomeres strong, or perhaps it's the absence of heavily processed cream-filled cookies that maintains dependable methylation.) "And "What can we learn from that?"

He's exploring how [social factors](#) influence those chromosomal features in Sardinia, Italy, and Ikaria, Greece—which along with Nicoya and Okinawa, Japan, comprise the four regions known as "blue zones" that are recognized for their populations' extreme longevity.

## **Blue zone, schmoo zone?**

The term blue zone was coined in 2000 by longevity researchers Michel Poulain, Ph.D., a senior researcher at the Estonian Institute for Population Studies at Tallinn University, Estonia; Giovanni Mario Pes, Ph.D., a senior researcher at the University of Sassari, Italy; and Daniel Buettner, a National Geographic fellow and one of Rehkopf's collaborators and friends.

The trio observed and described trends that seemed to exist in regions of the world where populations are longest lived, then marked them with blue circles on a map. But other academics doubted the scientific legitimacy of the trio's claims—particularly after other scientists and journalists claimed residents in other regions, such as areas in the Andes and Caucasus mountain ranges, also experienced exceptional longevity. (These claims were ultimately revealed to be based on incorrect information about residents' ages.)

Rehkopf, a molecular biologist-turned social epidemiologist, first heard about the impressively long lives of Costa Rican people when he was in graduate school at UC Berkeley. Even more intriguing to him was that the Costa Rican census and population-tracking system had stored generous amounts of meticulously gathered data from past decades. The information was systematically collected and verified via birth certificates, creating a trove of dependable, unmined data.

"That was key. It allowed for an unbiased approach to quantifying where people live the longest in Costa Rica and really let the data speak for

itself," said Rehkopf. As his interest in Costa Rica grew, he met a like-minded Costa Rican demographer by the name of Luis Rosero-Bixby, Ph.D., who was a research collaborator of Rehkopf's postdoctoral mentor. Some 16 years later, Rehkopf and Bixby are still close collaborators as they continue to survey the people of Nicoya.

When Rosero-Bixby and Rehkopf first teamed up in 2007, Nicoya was not yet a sanctioned blue zone, and questions of the blue zones' legitimacy still lingered.

The research, which was conducted in collaboration with the Costa Rican Longevity and Healthy Aging Study, revealed a "spatial variation of longevity" in Costa Rica, meaning some regions throughout the country were home to an exceedingly high number of healthy old people.

"To my knowledge, that was one of the first studies that really showed strong evidence to support the phenomenon," said Rehkopf.

In that study, Rehkopf and colleagues showed that Nicoyan people who were around 60 years or older were about 29% less likely to die at that age than people in the rest of Costa Rica. They also found, in 2013, that men benefited from living in the Nicoya blue zone more than women did. Within Nicoya, men are seven times more likely to live to 100 than men living in Japan, a country with a higher gross domestic product and a generally high overall average life span, their research showed.

[The 2013 study](#) also showed that rates of cardiovascular disease and high blood pressure—two ailments that disproportionately impact men—were significantly lower in Nicoyan men compared to Japanese men. "Or maybe it's because men just have more room to improve," Rehkopf said, referring to the comparatively lower life span of the average man.

The data was clear. Nicoya enjoyed a lower mortality rate than most the

world. It was time, Rehkopf and Rosero-Bixby decided, to go molecular.

## Time-telling telomeres

The 2013 study also revealed the first clues into what underpinned this lavish longevity: telomeres. Telomeres are nubs of DNA that cap both ends of our chromosomes, the structures of bundled-up DNA that contain our genetic information. Telomeres act as a sort of molecular buffer zone: As chromosomes replicate and split, the DNA at the ends is at risk of fraying and tangling. So instead of our genes withering away, telomeres protect the genetic information from degrading.

Once telomeres have worn away, the cell dies. So the longer the telomere, the longer a cell can live. Rehkopf, Rosero-Bixby and colleagues pulled at that thread, conducting further studies of Nicoyan people to examine the length of these protective caps in immune and blood cells.

Multiple studies have shown that telomeres act as a molecular marker of stress. One study evaluated telomere length in a group of adults who were tending to sick family members. Telomeres in this population were shorter compared to the average person's, age and gender aside. But when the family member recovered or care was no longer needed, [telomere length](#) returned.

Nicoyans, it turns out, have exceptionally lanky telomeres. Rehkopf and Rosero-Bixby conducted [another study in 2013](#) showing that, in immune cells, Nicoyan people have about 81 additional base pairs on their telomeres compared to people in the rest of Costa Rica. During replication, telomeres lose anywhere from 30 to 200 base pairs. Once the telomeres run out, the cell dies. So an extra 81 base pairs could mean a cell can undergo an additional three cycles of cell division before dying. "Telomere length can be seen as a measure of cellular age, which is

different from a person's calendar age," said Rehkopf. And, according to their telomeres, Nicoyans are young on the inside.

That doesn't mean that Nicoyan people feel no stress. But perhaps their social system and community is structured such that, when stressors arise, friends and family are nearby to support and weather the trouble together.

## **Maybe you're born with it, maybe it's methylation**

Some four years after their initial telomere analyses, Rehkopf and others turned their attention to a molecular phenomenon called methylation, which helps to regulate gene activity.

During methylation, molecules called methyl groups, made of one carbon and three hydrogen atoms, latch onto various genes. These accessories can rev up or subdue the genes' activity, and too much or too little activity can stir trouble. So can high variability, which equates to sloppy methylation. What's needed is methylation in moderation.

"When people age, two things happen: an increase in methylation variability, and a resulting imprecision in regulation of gene expression," said Rehkopf. That imprecision is what leads to aging and susceptibility to disease.

But not so much in Nicoyans: Elderly Nicoyans have a methylation pattern that reflects a younger person, particularly in their immune cells. Subsequent studies to analyze methylation in blood cells revealed that same trend—younger methylation.

Methylation, overall, is not set in stone. Environmental occurrences can change one's methylation pattern. (Past studies have shown that people who have experienced trauma have altered methylation patterns.) So

perhaps, suggested Rehkopf, a similar logic applies to communities in Nicoya, a rural place where societal norms are markedly different than say, a city in the United States: few cars, families who live together in multigenerational housing or in houses close to one another, and other ways of life that avoid big-city stressors.

Just last year, Rehkopf and others investigated how smoking impacts longevity in Nicoya, finding that people there who smoked had methylation patterns associated with accelerated aging. [Their findings](#) were published in *Scientific Reports*.

Youthful methylation patterns among elders were thought to be unique to Nicoyans—until Rehkopf conducted [a follow-up study](#) in Ikaria and Sardinia, published in November 2022 in *Frontiers in Aging*, revealing that some of the same telltale methylation patterns persisted in these zones too.

Rehkopf's study also found that Nicoyans have lower levels of CD8 T cells, a type of immune cell, which play a critical role in killing infected cells.

"Basically, the more mature CD8 cells a person has, the more wear and tear their immune system has seen," said Rehkopf. In other words, the immune systems of older Nicoyans are still fresh-faced and ready to take out infected or otherwise naughty cells.

Rehkopf plans to expand his sleuthing to the genetic realm. Past studies dismissed genetics as a root cause of the Nicoyan people's long life span. But Rehkopf and collaborator Michael Greicius, MD, a Stanford Medicine geneticist and neurologist, are teaming up to pressure test that idea. "I wonder whether past genetic studies of the population just weren't granular enough. We're using fine-grain sequencing to see if those findings really hold up," Rehkopf said.



## Make your own blue zone?

While the rest of the world marvels at the extra years of life among blue zone residents, Rehkopf said, the people, at least in Nicoya, don't pay much attention to their superior mortality stats. "They're just living their lives—walking their kids to school, visiting family within the community, and cooking simple, unprocessed meals."

So are Nicoyans born inoculated with the elixir of youth? Or do they make their own longevity? The likeliest explanation is both, said Rehkopf. Folks who move to Nicoya around retirement age don't suddenly tack years onto their lives. (Rehkopf and others conducted a study in 2013 showing that Nicoyans who see extended life spans are born and raised in Nicoya and spend their adult lives there too.) Also, Nicoyans who are born and raised in the region but move to another place for adulthood don't get the blue zone effect.

But that doesn't mean other people can't take lifestyle tips by examining the rural peninsula's way of life. Physically active lives; simple, clean cooking and diets that are high in fiber and lean protein, and low in fat and unprocessed ingredients; and community ties and support can all contribute to a microenvironment that replicates the behaviors, and maybe even the effects, seen in blue zones.

Nicoya isn't full of marathon runners or vegans. But the days of those who live there are filled with movement—for example, sweeping the front porch in the morning, walking kids to and from school, working on the farm, raising cattle, laundering by hand and making visits to family on foot. And, in Costa Rica, primary care doctors make home visits to families, meaning annual checkups or appointments are infrequently missed or forgotten.

Those behaviors, even if they're not sole contributors to healthy aging,

are vital—and it may even be possible to bundle them into a routine that creates one's own micro blue zone, said Rehkopf. "The social behaviors seen in blue zones are things we can all integrate into our everyday."

But even in Nicoya, some of them are starting to slip. "As more Western foods and modes of transportation become common in Nicoya, we're seeing the blue zone effect become more tenuous," said Rehkopf. It's still there—but the life expectancy of the population born around the 1940s and 1950s is dipping.

"These people are losing the advantage seen by previous generations," said Rosero-Bixby. "It's not uncommon to see people in Nicoya live to be in their 90s, but we're seeing that number slip back down into the 80s." It's not clear why, but levels of diabetes are increasing across Costa Rica—potentially one key indicator of change. If the trend continues, the "Nicoya effect" could be lost entirely over the next several decades.

That's not to say that all blue zones are on the way out. Nearly 6,000 miles away, in Denmark, several new hot spots for longevity are emerging. A report in 2018 pointed to some regions of the country seeing statistically longer life spans, raising the question of whether more blue zones are yet to be identified. Rehkopf suspects persistent activity, as opposed to spurts of rigorous exercise, might play a big role. Biking is the main form of transportation in Denmark; it's built into their culture and infrastructure.

"The four blue zones that exist weren't the result of an exhaustive search," said Rehkopf. "There may very well be others that aren't even on our radar."

**More information:** Andres Cardenas et al, Epigenome-wide association study and epigenetic age acceleration associated with cigarette smoking among Costa Rican adults, *Scientific Reports* (2022).

[DOI: 10.1038/s41598-022-08160-w](https://doi.org/10.1038/s41598-022-08160-w)

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