**outlook**


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**COVID-19 led to social isolation and stress as families were unable to enter care homes to visit elderly relatives.**

# How the COVID-19 pandemic might age us

## Infectious disease, loneliness and stress can affect cellular ageing, making us less healthy and shortening our lifespans. **By Emily Sohn**

As the COVID-19 pandemic continues, we might feel we're ageing faster than before. That's not as strange as it sounds. Accelerated ageing can result from several factors, some of which have been highlighted by the pandemic. Exposure to infectious diseases, chronic stress and loneliness can all affect the ageing process, exacerbating health conditions and shortening lives.

As scientists become more adept at measuring ageing in the body, however, it is becoming clear that some people are remarkably resilient to these and other stressors — an observation that has fuelled research into how life experience might slow the ageing process.

Until about 20 years ago, scientists thought ageing was unmodifiable and happened at the same rate for everyone, says Luigi Ferrucci, a geriatrician and epidemiologist at the US National Institute on Aging in Baltimore, Maryland. Although it did seem that some people remained healthier for longer than others who had lived for the same length of time, there seemed to be no way to change the physiological or cognitive declines that individuals experience as they get older.

That kind of thinking started to change in the 1980s, Ferrucci says, when researchers linked small genetic modifications in the worm *Caenorhabditis elegans* with substantially longer lifespans. This pointed to potential pathways for intervention[1]. Subsequent research identified a variety of genes that had similar effects through different mechanisms in mice and other mammals. Some genetic mutations have been associated with extreme longevity in people as well.

It's not just genes and signalling pathways that can affect the ageing process. A growing body of research published over the past two decades suggests that ageing can also be influenced by behavioural changes, such as calorie restriction and pharmacological interventions. These external factors can alter both the lifespan (how long someone lives) and the health span (how long they remain healthy).

And that has raised the tantalizing possibility that we might be able to slow the process. This would transform medicine, Ferrucci says.

Instead of dealing with health issues such as cardiovascular disease or cancer one at a time, an anti-ageing approach could address many health problems at once. "We still know very little about treating patients with complex multiple multimorbidity, which is truly the bulk of patients that come to medical observation," he adds.

A deeper understanding of the biology of ageing and its effects on disease susceptibility could lead to interventions to slow the ageing process, Ferrucci says. But scientists first need a reliable way to measure the rate of ageing.

One of the most promising approaches, epigenetics, emerged about a decade ago, when methyl groups were found to attach to DNA and regulate gene activity (see page S20). At specific sites in the genome, methyl groups accumulate in predictable patterns over time. In 2013, researchers at institutions including the University of California, Los Angeles, and Sichuan University in China developed algorithms that can calculate a person's epigenetic age based on these patterns[2,3].

These epigenetic clocks have since become more sophisticated, precise and predictive, Ferrucci says. With a sample of blood or tissue, scientists can now compare a person's cellular age with their chronological age. If their epigenetic age is older than their number of laps around the Sun would suggest, studies show a small but significant correlation with worse health, more pain and a higher risk of premature death, Ferrucci says.

Epigenetic age is not the only strategy that scientists are using. Ronald DePinho, a cancer-biology researcher at the University of Texas MD Anderson Cancer Center in Houston, says ageing is associated with a suite of degenerative states including cellular death or senescence, tissue inflammation and metabolic dysfunction. These result from breakdowns in mitochondrial function, cellular communication, DNA repair and other processes.

Extensive research over decades by DePinho and colleagues[4], among others, has linked these hallmarks of ageing to dysfunction in the telomeres at the ends of chromosomes. Telomeres get predictably shorter over a lifetime, and some scientists use their length as a measure of cellular age.

The search for biomarkers of ageing also includes proteomics, as researchers look for proteins associated with ageing-related processes such as inflammation and senescence. Ferrucci and colleagues have identified 651 relevant proteins, and in one 2020 study found a 76-protein "proteomic age signature" that predicted chronic diseases and mortality[5].

As the number of biological clocks grows, "we are refining them until we find something that is good enough for clinical utilization," Ferrucci says. They might identify people who are on an ageing fast-track and might benefit from interventions. Or they could be used to assess whether treatments are helping to slow the ageing process. A reliable clock for measuring the cellular march of time could also tell us how much the pandemic has aged us so far.

## The infection connection

Genetic variations influence how quickly people age, but behaviours and life events can also influence epigenetic age — including exposure to infection. Studies suggest that infection with HIV, for example, accelerates the ageing and death of immune cells[6]. Ferrucci thinks the SARS-CoV-2 virus that causes COVID-19 can also result in chronic inflammation and accelerated biological ageing.

It was clear early in the pandemic that older people, especially those with underlying medical conditions, are particularly likely to experience uncontrolled inflammatory responses called cytokine storms, as well as severe symptoms and death, as a result of COVID-19. This might be partly because, as people age, they are more likely to have high levels of inflammatory markers in their blood, Ferrucci says. One hypothesis, known as inflammaging, holds that this inflammation contributes to elevated risks[7] not just for a severe case of COVID-19, but also for cardiovascular disease, kidney disease, dementia, cancer and other problems that become more common with age.

In COVID-19, inflammation seems to arise through several pathways, including cellular senescence, which, DePinho says, leads to a cascade of immune responses that include the secretion of cytokines and other inflammatory molecules. Cellular senescence has also been implicated in cancer, osteoarthritis and other ageing-related diseases.

Those processes can affect people of all ages, Ferrucci says. When inflammatory reactions to the COVID-19 virus are high, the immune system can become less resilient in the long term, potentially leaving some people less able to resist the effects of ageing. "Their compensatory mechanisms have already been consumed by fighting COVID-19," he adds.

## Don't stress

Even for people who never get infected with the virus itself, the COVID-19 pandemic has been stressful — particularly for those who were already under stress, says Laura Fonken, a neuroscientist at the University of Texas at Austin. Job losses, concerns about health, and the illnesses and deaths of loved ones have added considerable anxiety to the disease itself.

With schools closed for months at a time, parents have struggled to supervise their kids while doing their own jobs, says psychologist Erika Wolf of Boston University School of Medicine and the National Center for PTSD, part of the US Department of Veterans Affairs.

Stress can also contribute to accelerated ageing, research suggests. When experienced over a long period of time, it has been linked with heart disease, diabetes and the spread of cancer, as well as other chronic diseases. And physiological responses can start young.

Children from poor socio-economic backgrounds undergo puberty earlier than those from wealthier backgrounds, studies show, and early puberty has been associated with a variety of health problems and shorter lifespans. By early adulthood, exposure to trauma and conditions such as post-traumatic stress disorder (PTSD) can start to show up in the form of ageing-related diseases.

By studying a cohort of US military veterans in their early 30s who served in Iraq and Afghanistan, Wolf has documented an elevated rate of metabolic syndrome. Symptoms include obesity and high blood pressure, which in turn increase the risk of diabetes, heart problems and Alzheimer's disease. Other studies have found higher rates of metabolic syndrome, early-onset Alzheimer's and other forms of dementia in veterans with PTSD.

> **"Their compensatory mechanisms have already been consumed by fighting COVID-19."**

By using epigenetic clocks, Wolf and colleagues have linked PTSD with higher-than-expected epigenetic age in young veterans. Among PTSD symptoms, hypervigilance, anger and poor sleep are especially predictive of accelerated ageing, their data show. Veterans with signs of accelerated epigenetic ageing also perform worst in cognitive tests and show more declines in the structural integrity of the brain areas responsible for executive functioning than veterans with less cellular ageing.

Studies of stressed animals show that the immune cells in their brains start to look like those you would expect to see in an ageing brain. They are prone to produce inflammation when stimulated, says Fonken. Long-term, low-grade inflammation can affect cognitive function — and some data suggest that COVID-19 can too.

To investigate the link between stress and the brain, Wolf and colleagues are using magnetic resonance imaging (MRI) and magnetic resonance spectroscopy to study a group of

veterans with an average age of 65 who they have been following for 15 years. The researchers are measuring neuroinflammation and assessing memory, executive functioning and other indicators of cognitive health. They hope to find ways of predicting who is most at risk of cognitive decline and accelerated ageing as a result of trauma and chronic stress. Because the pandemic started during the study, she says, it might reveal how the experience is affecting the ageing process.

Data already suggest that the pandemic has exacerbated the links between stress and ageing. When it began, Wolf and colleagues tested veterans and found more-severe PTSD symptoms and problems with alcohol misuse. In turn, those with symptoms of alcohol misuse were more likely to report having had COVID-19. The results, which have been submitted for publication, suggest that people can be caught in a cycle of chronic stress and worsening health. "There is this idea that some people are at greater risk of accelerated ageing in response to the pandemic," she says, "and it may have to do with the fact that they've already got this process under way."

It is not yet clear how stress might accelerate ageing, but some research has linked chronic stress with shortened telomere length. This seems likely because elevated levels of the stress hormone cortisol promote telomere-damaging pathways, especially over years or decades, DePinho says. A pivotal early study from 2004 showed[8] that premenopausal women with the highest levels of perceived stress had telomeres short enough to represent at least a decade of excessive ageing compared with women who reported low levels of stress. A 2016 study[9] by some of the same authors, including psychologist Elissa Epel at the University of California, San Francisco, included 16 years of data from more than 4,500 people. It found that adverse events in childhood, such as prenatal exposure to maternal stress and repeated experiences of abuse, led to more rapid shortening of telomeres in adulthood. Each adverse experience increased the risk of having short telomeres by 11%.

Shortened telomeres hinder the body's ability to repair damage. "To put this in the COVID context, chronic unrelenting stress can further accelerate the ageing process," DePinho says, "which would lead to diminished resilience."

The links are complex, Wolf adds. Her work has found connections between accelerated ageing and behaviours that are associated with PTSD, such as alcohol use disorder and poor nutrition, suggesting that the interaction between stress and behaviour is what influences biological processes.

Genetics matters too. PTSD is more likely to be associated with accelerated epigenetic ageing in people with a certain variation in a gene called *Klotho*, which is named after a Greek goddess who, according to mythology, spun the web of time and determined the span of human life.

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**Klotho (right) was one of the Three Fates in Greek mythology and spun the thread of life.**

## Home alone

By mid-April in 2020, 89 countries had instituted lockdowns, affecting more than one-third of the world's population, according to a 2020 paper[10] by Bei Wu, a gerontologist at New York University. Older people are more likely to experience serious symptoms from COVID-19, so they were particularly prone to isolation during lockdowns. Nursing homes were closed to visitors, and many health services and social programmes shut down. Before the pandemic, 43% of older adults in the United States reported feeling lonely, according to a 2020 report[11] from the National Academy of Sciences, Engineering and Medicine.

All that time alone might be another risk factor for accelerated ageing. Wu and others have linked social isolation and loneliness with a 50% greater chance of developing dementia, a 29% higher risk of incident coronary heart disease, and a 32% greater risk of stroke[12] — all of which are ageing-related diseases. Isolation and loneliness have also been linked with higher rates of heart disease, obesity, depression, anxiety, high blood pressure, cognitive decline and premature death.

Social isolation is an important strategy for slowing the spread of infectious disease, but it could make it harder for people to recover from COVID-19 if they are infected, DePinho says. Several studies of mice found that isolation after a stroke leads to worse outcomes, both physically and mentally. The stress of being alone is probably a major cause.

## Live long and prosper

Despite the many ways that stress, isolation, disease and other pandemic-era worries can affect health, some people go on to live long and healthy lives after enduring extreme hardship. Among these are some Holocaust survivors who have lived into their 90s and beyond. Some scientists are keen to find out what makes these people so resilient — and how the rest of us might cultivate it. "People can experience the exact same trauma and have very different outcomes," Fonken says.

There may eventually be hope for counteracting the rapid ageing that many people feel they are experiencing in this stressful time. In research with mice, DePinho's group and others have found that removing senescent cells can extend lifespan by more than one-third. For now, experts recommend a variety of evidence-based lifestyle strategies to combat the ageing effects of the pandemic.

Just 15 minutes of exercise a day can increase your life expectancy by five years and decrease the incidence of age-related diseases such as Alzheimer's, cancer and diabetes by 14%, DePinho says. Meditating can decrease cortisol levels, while maintaining a healthy weight can calm the inflammatory response, and a diet rich in fruits and vegetables can counteract the effects of oxidative stress. Not smoking helps too, and getting enough high-quality sleep can counteract rapid ageing.

"It shouldn't be an all doom-and-gloom story," Wolf says. "There's a lot of animal literature suggesting that exercise and especially nutrition make a big impact on cellular ageing measures. I think there are opportunities to intervene in this process."

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