Younger Adults Caught in COVID-19 Crosshairs as Demographics Shift

Jennifer Abbasi

Shauna Gray and Benner Hall probably aren’t the picture of what coronavirus disease 2019 (COVID-19) looks like in most people’s minds. They’re young and fit with no underlying health issues. And yet the illness flattened the Brooklyn couple, both aged 41 years at the time, in mid-March. Gray first noticed symptoms on March 18. Three days later, her husband felt sick.

“I know these dates exactly because they will forever be burned into my memory,” Gray said in a recent interview.

At first Gray assumed that the pair’s young son, who had recently had influenza, had passed it on to them. At the time, patients with COVID-19 had begun to report losing their sense of taste. Gray finally realized she had the disease when the apple juice she was craving “just tasted like ‘wet’ and water tasted like metal.” The couple couldn’t get polymerase chain reaction testing at the height of New York City’s outbreak, but Gray said both have since tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies.

Their illnesses didn’t play out like the flu she initially thought they had. By the end of about 10 terrible days, most of the infection’s acute symptoms—fever, headache, chills, night sweats—had passed, but the chest tightness, shortness of breath, and crushing fatigue continued. Recovery came in dribs and drabs. It took about 6 weeks for Hall’s energy level to get back to 100%. Three months passed before Gray’s tiredness fully subsided and she could walk up a flight of stairs without feeling winded.

On the other side of the country, Garrett Salzman, MD, a 30-year-old surgical resident at the University of California-Los Angeles, began to feel sick on March 16. A few days later, the body aches began. “I couldn’t sleep because the pain was so bad,” he said. “Every joint, every muscle in your body just feels like it’s being placed in a searing hot iron. It was pretty miserable.”

Before the pandemic, the former college athlete’s only health complaint had been exercise-induced asthma. On March 27, after feeling better for a day, he developed profound shortness of breath. “It was literally like I had been hit by a train,” he recalled in an interview. A chief surgical resident in full personal protective equipment picked him up from his apartment and brought him to his own hospital’s emergency department. There, another surgical colleague oversaw the start of his care and called his parents.

Salzman was admitted to the general ward, where he was given fluids. His condition improved and he went home 3 days later. But the body aches, fatigue, and tachycardia persisted for weeks. And like Gray, it was about 3 months before his strength fully returned. Still, not everything is back to normal. His near-complete loss of smell may be permanent, physicians have told him.

Healthy young people like Salzman, Gray, and Hall were never risk free, but most COVID-19 cases identified early on were in older adults and people with chronic health conditions, who are much more likely to have severe disease and to die. As a result, research efforts, public health messaging, and public awareness had largely focused on those high-risk groups.

But recent national data show that new infections have increased in younger adults, an uptick that isn’t fully attributable to increased testing in these groups. Although the majority of these cases likely will be asymptomatic or mild, physicians and survivors say that’s not the full picture. COVID-19 on occasion kills younger people. The deaths may be relatively rare, but some nonfatal symptomatic cases can be hugely disruptive and even life altering.

The demographic shift brings with it a simple calculus: As more younger adults become infected, increasing numbers of them could experience a debilitating illness with potential long-term health effects. Public health experts and physicians have sounded the alarm that younger groups need to take the virus more seriously—not just to protect their loved ones and communities but for their own health, as well. At the same time, research is starting to offer up hints as to why some young people fall prey to severe COVID-19.

The Pandemic’s Changing Face

An October 2 Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report documented COVID-19’s demographic changes. Between May
and July, the median age of confirmed US cases fell from 46 years to 37 years. The pandemic’s age distribution had already shifted by June, when new cases were highest among people aged 20 through 29 years. From August 2 to September 5, the weekly incidence among people aged 18 through 22 years roughly doubled from 10.5% to 22.5% of total new cases, some of which was likely due to college students going back to school.

Of the almost 7 million COVID-19 cases included in the CDC’s COVID Data Tracker, about 76% have occurred among adults younger than 65 years, with 18- through 29-year-olds making up the largest chunk. The hospitalization and death rates continue to be far greater among seniors but, importantly, not all younger adults experience mild disease. As of late October, death certificate data show that COVID-19 has killed almost 45 000 people aged 15 through 64 years, including about 6300 adolescents and adults younger than 45 years.

“While young people are lower risk, they’re not zero risk,” Jon Cunningham, MD, a cardiovascular medicine fellow at Brigham and Women’s Hospital, said in an interview. “People should take that into account in making decisions about their behavior and public health.”

Cunningham and his colleagues reported in JAMA Internal Medicine that even the youngest adults who are hospitalized with the disease may not be spared from poor outcomes. He analyzed data from 3222 patients aged 18 to 34 years who were admitted to US hospitals. More than one-fifth of them required intensive care, one-tenth required mechanical ventilation, and 88, or 2.7%, died.

“Most young people won’t get sick enough to need to go to the hospital, but some will, and those who do face reasonably high, substantial risks of serious adverse outcomes that occur in the setting,” Scott Solomon, MD, a Harvard Medical School professor and the study’s senior author, said in an interview.

As Gray and Hall’s stories show, milder cases in nonseniors can be worrisome too, especially when symptoms linger for weeks to months. In late July, the CDC published a survey of 292 adults with COVID-19 who were not hospitalized. About one-fourth of respondents aged 18 through 34 years and about one-third of those aged 35 through 49 years had not fully regained their health 2 to 3 weeks after their diagnosis. The most common ongoing symptoms included cough, fatigue, congestion, and shortness of breath. To put this into perspective, the study’s authors pointed out that more than 90% of outpatients with influenza recover within about 2 weeks.

What’s more, 1 in 5 outpatients in the younger age range with no health problems reported lingering symptoms in the CDC report. The authors’ conclusion: “COVID-19 can result in prolonged illness, even among young adults without underlying chronic medical conditions.”

Despite data points like these, “we do not have a really good grasp of the impact of this disease on otherwise young, healthy people,” Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), said in an interview. Fauci said the prevalence, duration, and severity of post-COVID syndrome among younger adults needs fleshing out.

He also cited a study of 100 German patients who had recently recovered from COVID-19. Most had cardiac involvement and ongoing myocardial inflammation on magnetic resonance imaging, independent of preexisting conditions and COVID-19 severity. Their average age was 49 years. “It could go away and be nonsignificant or it could wind up being a chronic problem,” Fauci said of the abnormalities. “I just think we have to keep an open mind about this.”

As the understanding of COVID-19 in younger individuals grows, physicians should not dismiss their symptoms, stressed Caspar van der Made, MD, an internal medicine resident at the Radboud University Medical Center in the Netherlands, who is studying genetic factors that predispose young people to severe disease. “We should not underestimate the signs of COVID-19 in these young individuals as we come to learn more about the subclinical effects of the disease and post-COVID morbidity,” he said in an email.

Younger Adults’ Risk Factors
Older adults have heightened COVID-19 risks for 2 main reasons. First, immunity wanes with advanced age. Second, health problems mount with the years, increasing a person’s risks of developing COVID-19 complications. But the cause of serious disease among younger people with presumably strong immune systems is more perplexing.

“We do not know why younger adults without these comorbidities sometimes develop severe COVID-19,” Michael Satlin, MD, an infectious disease specialist at Weill Cornell Medicine, noted via email.

As with seniors, younger adults with preexisting health conditions, including chronic kidney disease, heart disease, obesity, and type 2 diabetes, are more vulnerable to severe COVID-19. In addition, the CDC now says that anyone who is overweight, with a body mass index (BMI) between 25 and 30, also might have heightened risks.

Elevated BMI is one of the more common health problems that plague younger people, and it’s “fundamentally one of the most important risk factors for hospitalization at young age” for COVID-19, said Ajay Bhasin, MD, an assistant professor of hospital medicine at Northwestern University’s Feinberg School of Medicine. He and his colleagues recently found that younger patients hospitalized with COVID-19 had higher BMI than older ones, with the very youngest carrying the most extra weight.

In the JAMA Internal Medicine study, morbid obesity, along with hypertension and diabetes, were frequent comorbidities among the young, hospitalized patients. That study also reinforced the understanding that race and ethnicity are associated with more serious illness. More than half of the patients were Black or Hispanic, demonstrating that the disproportionate burden of severe COVID-19 borne by people of color includes those in their 20s and 30s.

Younger adults’ health-related behaviors also influence their susceptibility to the infection and to poor outcomes. In a national survey that included young adults, vaping and dual use of e-cigarettes and cigarettes were major underlying risk factors for developing COVID-19.

And as with any infection, there’s also individual variability. Although not every young person fares well, “not every 80-year-old who gets COVID does poorly either,” said Betsy Herold, MD, a pediatric infectious disease specialist at the Albert Einstein College of Medicine, who is investigating age-related differences in COVID-19 immune responses.

Michael Sneller, MD, who studies immunoregulation at the NIAID, said that the peculiarities of each person’s unique immune system influence their susceptibility to SARS-CoV-2 and their disease severity if they become infected. After all, no 2 immune
systems are built precisely alike. “All infections are kind of a race—most of the time the immune system wins, but sometimes the virus does,” Sneller said in an interview. “Some people may have some undefined selected defects in their immune system that allow the virus to get a foothold.”

Researchers worldwide are working to uncover those defects, while others are looking for genetic variations or other mechanisms that could underpin them. “There are likely a combination of genetic and nongenetic factors for every individual,” Ben Solomon, MD, clinical director of the National Human Genome Research Institute, said in an email. “I am confident that genetics plays an overall role.”

An Explanation Takes Shape
According to Sneller, the story that’s shaping up is that severe COVID-19 may result when an underwhelming initial immune response in the nasal passages fails to control the virus. This allows the virus to grow to high levels and spread to the lungs where it causes an overly exuberant inflammatory reaction.

“It’s that inflammatory response to the virus that’s really associated with having progressive disease and developing what’s called acute respiratory distress syndrome or ARDS,” Herold said in an interview. “That’s somewhat perhaps unique to this virus—the amount of inflammation that we’re seeing—and that makes this virus different from influenza.”

Type I interferons—signaling cytokines that thwart viral replication—are emerging as key players. Research suggests that the novel coronavirus has developed mechanisms to evade their response, which is impaired in patients with severe COVID-19. Investigators are also homing in on the inflammatory cytokines involved in severe disease. High levels of 3 cytokines predicted survival in a study of patients hospitalized with COVID-19 at New York’s Mount Sinai Health System. One of them, interleukin 6, was significantly associated with survival in the subset of patients aged 50 years or younger, according to Sacha Gnjatic, PhD, an immunologist at the Icahn School of Medicine at Mount Sinai in New York City and the study’s senior author. “So it is possible that higher inflammatory cytokines also contribute to poorer survival even within younger patients,” he said in an email.

For some people, genetic changes could underlie a dysregulated immune response to the virus. And “in young patients that are otherwise healthy, the role of genetics will be more apparent,” van der Made said.

He led a genetic study of 2 pairs of previously healthy brothers with COVID-19 ranging in age from 21 to 32 years who all required mechanical ventilation in the intensive care unit (ICU). One of the young men died. All 4 turned out to have rare loss-of-function variants in the TLR7 gene, which van der Made’s experiments showed were associated with impaired type I and II interferon responses. The gene is located on the X chromosome, of which males only have 1. “Therefore, we think that a male carrier of such a variant cannot effectively fight off the virus in its early stages, causing the virus to accumulate with an ensuing hyperinflammatory response and pneumonia,” van der Made said in an email.

Another research team has found rare loss-of-function variants and more common autoantibodies underlying life-threatening COVID-19 pneumonia in all ages. The autoantibodies, which target type I interferons, were present in the blood of about 3% of women and about 13% of men in the study, which involved almost 1000 patients. None of the more than 600 people with asymptomatic or mild SARS-CoV-2 infections had the autoantibodies.

The search continues for other “genetic immunological causes in the young and healthy who all of a sudden are in the ICU,” one of the study’s senior authors, Jean-Laurent Casanova, MD, PhD, head of the St Giles Laboratory of Human Genetics of Infectious Diseases at The Rockefeller University, said in an interview. “We hope to crack this problem in the coming months, years, decades.”

And yet there’s also another, less complex contributor to an individual’s risk, experts say. “I think underlying all of this would probably be inoculum effect,” Sneller said. Something as simple as the amount of virus a person is exposed to could affect their infection’s course, he explained.

This might account for some of the severe illness and death among healthy, young medical professionals in the pandemic’s early days. “One hypothesis is that very high levels of exposure to the virus (when cases were not quickly identified and personal protective equipment was not abundant) led to these severe cases, but more research is needed to confirm this,” Satlin said.

This also means that wearing a mask and using social distancing to reduce viral exposure could make the difference between a mild case of COVID-19 and an ICU stay, even for a healthy young person. “My message would really be to take it very seriously,” Salzman said.

Note: Source references are available through embedded hyperlinks in the article text online.