



Many very sick COVID-19 patients, like some in this Brazilian intensive care unit, have obesity.

IN DEPTH

COVID-19

Why obesity worsens COVID-19

Even people in the overweight category face higher risk of serious disease

By Meredith Wadman

This spring, after days of flulike symptoms and fever, a man arrived at the emergency room at the University of Vermont Medical Center. He was young—in his late 30s—and adored his wife and small children. And he had been healthy, logging endless hours running his own small business, except for one thing: He had severe obesity. Now, he had tested positive for COVID-19 and was increasingly short of breath.

He was admitted directly to the intensive care unit (ICU) and was on a ventilator within hours. Two weeks later, he died.

“He was a young, healthy, hardworking guy,” recalls MaryEllen Antkowiak, a pulmonary critical care physician who is medical director of the hospital’s ICU. “His major risk factor for getting this sick was obesity.”

Since the pandemic began, dozens of studies have reported that many of the sickest COVID-19 patients have been people with obesity. In recent weeks, that link has come into sharper focus as large new population studies have cemented the association and demonstrated that even people who are merely overweight are at higher risk. For example, in the first metaanalysis of its kind, published on 26 August in *Obesity Reviews*, an international team of research-

ers pooled data from scores of peer-reviewed papers capturing 399,000 patients. They found that people with obesity who contracted SARS-CoV-2 were 113% more likely than people of healthy weight to land in the hospital, 74% more likely to be admitted to an ICU, and 48% more likely to die.

A constellation of physiological and social factors drives those grim numbers. The biology of obesity includes impaired immunity, chronic inflammation, and blood that’s prone to clot, all of which can worsen COVID-19. And because obesity is so stigmatized, people with obesity may avoid medical care.

“We didn’t understand early on what a major risk factor obesity was. ... It’s not until more recently that we’ve realized the devastating impact of obesity, particularly in younger people,” says Anne Dixon, a physician-scientist who studies obesity and lung disease at the University of Vermont. That “may be one reason for the devastating impact of COVID-19 in the United States, where 40% of adults are obese.”

People with obesity are more likely than normal-weight people to have other diseases that are independent risk factors for severe COVID-19, including heart disease, lung disease, and diabetes. They are also prone to metabolic syndrome, in which blood sugar levels, fat levels, or both are unhealthy and

blood pressure may be high. A recent study from Tulane University of 287 hospitalized COVID-19 patients found that metabolic syndrome itself substantially increased the risks of ICU admission, ventilation, and death.

But on its own, “BMI [body mass index] remains a strong independent risk factor” for severe COVID-19, according to several studies that adjusted for age, sex, social class, diabetes, and heart conditions, says Naveed Sattar, an expert in cardiometabolic disease at the University of Glasgow. “And it seems to be a linear line, straight up.”

The impact extends to the 32% of people in the United States who are overweight. The largest descriptive study yet of hospitalized U.S. COVID-19 patients, posted as a preprint last month by Genentech researchers, found that 77% of nearly 17,000 patients hospitalized with COVID-19 were overweight (29%) or obese (48%). (The Centers for Disease Control and Prevention defines overweight as having a BMI of 25 to 29.9 kilograms per square meter, and obesity as a BMI of 30 or greater.)

Another study captured the rate of COVID-19 hospitalizations among more than 334,000 people in England. Published last month in the *Proceedings of the National Academy of Sciences*, it found that although the rate peaked in people

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with a BMI of 35 or greater, it began to rise as soon as someone tipped into the overweight category (see graphic, below). “Many people don’t realize they creep into that overweight category,” says first author Mark Hamer, an exercise physiologist at University College London.

The physical pathologies that render people with obesity vulnerable to severe COVID-19 begin with mechanics: Fat in the abdomen pushes up on the diaphragm, causing that large muscle, which lies below the chest cavity, to impinge on the lungs and restrict airflow. This reduced lung volume leads to collapse of airways in the lower lobes of the lungs, where more blood arrives for oxygenation than in the upper lobes. “If you are already starting [with] this mismatch, you are going to get worse faster” from COVID-19, Dixon says.

Other issues compound these mechanical problems. For starters, the blood of people with obesity has an increased tendency to clot—an especially grave risk during an infection that, when severe, independently peppers the small vessels of the lungs with clots (*Science*, 5 June, p. 1039). In healthy people, “the endothelial cells that line the blood vessels are normally saying to the surrounding blood: ‘Don’t clot,’” says Beverley Hunt, a physician-scientist who’s an expert in blood clotting at Guy’s and St. Thomas’ hospitals in London. But “we think that signaling is being changed by COVID,” Hunt says, because the virus injures endothelial cells, which respond to the insult by activating the coagulation system.

Add obesity to the mix, and the clotting risk shoots up. In COVID-19 patients with obesity, Hunt says, “You’ve got such sticky blood, oh my—the stickiest blood I have ever seen in all my years of practice.”

Immunity also weakens in people with obesity, in part because fat cells infiltrate the organs where immune cells are produced and stored, such as the spleen, bone marrow, and thymus, says Catherine Andersen, a nutritional scientist at Fairfield University. “We are losing immune tissue in exchange for adipose tissue, making the immune system less effective in either protecting the body from pathogens or responding to a vaccine,” she says.

The problem is not only fewer immune cells, but less effective ones, adds Melinda Beck, a co-author of the *Obesity Reviews* metaanalysis who studies obesity and immunity at the University of North Carolina, Chapel Hill. Beck’s studies of how obese mice respond to the influenza virus demonstrated that key immune cells called T cells “don’t function as well in the obese state,” she says. They make fewer molecules that help destroy virus-infected cells, and the

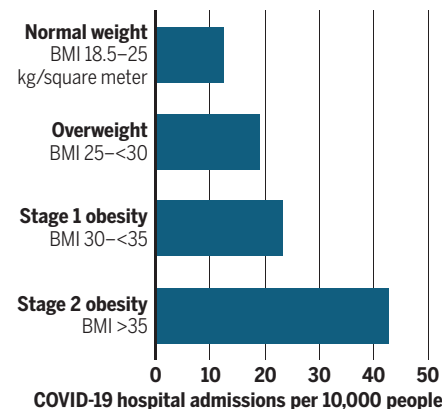
corps of “memory” T-cells left behind after an infection, which is key to neutralizing future attacks by the same virus, is smaller than in healthy weight mice.

Beck’s work suggests the same thing happens in people: She found that people with obesity vaccinated against flu had twice the risk of catching it as vaccinated, healthy weight people. That means trials of vaccines for SARS-CoV-2 need to include people with obesity, she says, because “coronavirus vaccines may be less effective in those people.”

Beyond an impaired response to infections, people with obesity also suffer from chronic, low-grade inflammation. Fat cells secrete several inflammation-triggering chemical messengers called cytokines, and more come from immune cells called macrophages that sweep in to clean up dead and dying fat cells. Those effects may compound the runaway cytokine activity that

The danger of extra kilos

Among 334,000 people in England this spring, the chances of being hospitalized with COVID-19 increased steadily with their body mass index (BMI).



characterizes severe COVID-19. “You end up causing a lot of tissue damage, recruiting too many immune cells, destroying healthy bystander cells,” says Ilhem Messaoudi, an immunologist who studies host responses to viral infection at the University of California, Irvine. Of the added risk from obesity, she adds: “I would say a lot of it is immune-mediated.”

The severity of COVID-19 in people with obesity helps explain the pandemic’s disproportionate toll in some groups. In American Indians and Alaska Natives, for example, poverty, lack of access to healthy food, lack of health insurance, and poor exercise opportunities combine to render “rates of obesity ... remarkably high,” says Spero Manson, a Pembina Chippewa who is a medical anthropologist at the University of Colorado’s School of Public Health.

And obesity “is connected to all these other [illnesses], such as diabetes and cardiovascular disease, rendering us susceptible” to severe COVID-19, Manson says.

In addition, a large body of literature shows that people with obesity may delay seeking medical care due to fear of being stigmatized, increasing their likelihood of severe disease or death. “Patients that experience weight stigma are less likely to seek care and less likely to seek follow up because they don’t feel welcome in the health care environment,” says Fatima Cody Stanford, an obesity medicine physician-scientist at Harvard Medical School and Massachusetts General Hospital.

COVID-19-specific research on this question is urgently needed, she adds. “We don’t know how many people are dying in the community that are never making it in,” Stanford says. “Maybe that was [due] to their weight or to their race, the two most prevalent forms of stigma in the U.S.”

For people with obesity, the extra risk adds a psychological burden, says Patty Nece, vice chair of the Obesity Action Coalition. “My anxiety is just totally ramped up,” she says, adding that because of stress eating she’s recently regained 30 of the 100 pounds she lost before the pandemic. “You have the general anxiety of this pandemic ... and then you layer on top of it: ‘You in particular, you could get really sick.’”

Data on how to treat COVID-19 patients with obesity are scant. Published evidence supports giving such patients higher doses of anticoagulants, says Scott Kahan, an obesity medicine physician who directs the National Center for Weight and Wellness. But very little is known about whether and how to adjust other treatments such as remdesivir and dexamethasone, partly because patients with obesity “are often excluded from clinical trials,” he says. He urges that COVID-19 treatment trials include people with high BMIs wherever possible.

People with obesity should take extra care to avoid getting sick, Messaoudi says. “If you are a person with obesity, be extra, extra cautious,” she says. “Wear your mask. Wash your hands. Avoid large gatherings.”

In addition, exercising and, separately, losing even a little weight can improve the metabolic health of a person with obesity, and, in doing so, reduce their chances of developing severe COVID-19 if they become infected, says Stephen O’Rahilly, a physician-scientist who directs the MRC Metabolic Diseases Unit at the University of Cambridge. “If you’re 300 pounds, even losing a modest amount is likely to have a disproportionate benefit on how well you do with coronavirus infection. You don’t have to become a slim Jim to benefit.” ■

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