

Insulin resistance doubles risk of major depressive disorder, study finds

September 23 2021



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Stanford Medicine scientists have linked insulin resistance to an increased risk of developing major depressive disorder.

"If you're [insulin](#)-resistant, your risk of developing [major depressive disorder](#) is double that of someone who's not insulin-resistant, even if you've never experienced depression before," said Natalie Rasgon, MD, Ph.D., professor of psychiatry and [behavioral sciences](#).

Upward of 1 in 5 Americans experiences major depressive disorder sometime during their lives. Symptoms include unremitting sadness, despair, sluggishness, sleep disturbances and loss of appetite. Some factors contributing to this deeply debilitating disease—childhood traumas, loss of a loved one or the stresses of the COVID-19 pandemic, for example—are things we can't prevent. But insulin resistance is preventable: It can be reduced or eliminated by diet, exercise and, if need be, drugs.

The researchers' findings are described in a study to be published online Sept. 22 in the *American Journal of Psychiatry*. Rasgon shares senior authorship of the study with Brenda Penninx, MD, Ph.D., professor of psychiatric epidemiology at the University of Amsterdam Medical Center. The study's lead author is Kathleen Watson, Ph.D., a postdoctoral scholar in Rasgon's group.

A common but silent condition

Studies have confirmed that at least 1 in 3 of us is walking around with insulin resistance—often without knowing it. The condition does not arise from a deficiency in the pancreas's ability to secrete insulin into the bloodstream, as occurs in Type 1 diabetes, but because of the decreased ability of cells throughout the body to heed this hormone's command.

Insulin's job is to tell our cells it's time for them to process the glucose that's flooding our blood due to our dietary intake of it, its manufacture in our liver or both. Every cell in the body uses glucose as fuel, and each of those cells has receptors on its surface that, on binding to insulin,

signals the cell to ingest the precious energy source. But an increasing proportion of the world's population is insulin-resistant: For various reasons—including excessive caloric intake, lack of exercise, stress and not getting enough sleep—their insulin receptors fail to bind to insulin properly. Eventually, their blood-sugar levels become chronically high. Once those levels stay above a certain threshold, the diagnosis is Type 2 diabetes, a treatable but incurable condition that can lead to cardiovascular and cerebrovascular disorders, neuropathy, kidney disease, limb amputations and other detrimental health outcomes.

Associations between insulin resistance and several mental disorders have already been established. For example, it's been shown that about 40% of patients suffering from mood disorders are insulin-resistant, Rasgon said.

But these assessments have been based on cross-sectional studies—snapshots of populations at a single point in time. The question of whether one event was the cause or the result of the other—or whether both were results of some other causal factor—are best resolved by longitudinal studies, which typically track people over years or even decades and can determine which event came first.

As a part of a multi-institutional collaboration within a research network Rasgon established in 2015, the scientists obtained data from an ongoing longitudinal study monitoring more than 3,000 participants in scrupulous detail to learn about the causes and consequences of depression: the Netherlands Study of Depression and Anxiety. Rasgon is the Stanford principal investigator, and Penninx is the overall principal investigator.

"The Dutch study, with its meticulous monitoring of a large subject population for nine years and still climbing, presented a great opportunity for us," Watson said.

Determining insulin resistance

The Stanford team analyzed data from 601 men and women who served as control subjects for the Netherlands study. At the time of their enrollment, they'd never been troubled by depression or anxiety. Their average age was 41 years.

The team measured three proxies of insulin resistance: fasting blood glucose levels, waist circumference, and the ratio of circulating triglyceride levels to those of circulating high-density lipoprotein—or HDL, known as "good" cholesterol.

They probed the data to see if the subjects found to be insulin-resistant had a heightened nine-year risk of developing major depressive disorder. By all three measures, the answer was yes: They discovered that a moderate increase in insulin resistance, as measured by the triglyceride-to-HDL ratio, was linked to an 89% increase in the rate of new cases of major depressive disorder. Similarly, every 5-centimeter increase in abdominal fat was related to an 11% higher rate of depression, and an increase in fasting plasma glucose of 18 milligrams per deciliter of blood was associated with a 37% higher rate of depression.

"Some subjects were already insulin-resistant at the study's start—there was no way to know when they'd first become insulin-resistant," Watson said. "We wanted to more carefully determine how soon the connection kicks in."

So, the researchers restricted the next phase of their analysis to the roughly 400 subjects who, in addition to never having experienced major depression, also showed no sign of [insulin resistance](#) at the study's onset. Within the first two years of the study, nearly 100 of these participants became insulin-resistant. The researchers compared this group's likelihood of developing major depressive disorder in the next seven

years with that of the participants who hadn't yet become insulin-resistant at the two-year point.

While the number of participants was too small to establish statistical significance for waist circumference and the triglyceride-to-HDL ratio, the results for fasting glucose were not only statistically significant—meaning unlikely to have arisen by chance—but clinically meaningful—that is, important enough to worry about: Those developing prediabetes within the first two years of the study had 2.66 times the risk for major depression by the nine-year follow-up milestone, compared with those who had normal fasting-glucose test results at the two-year point.

The bottom line: Insulin resistance is a strong risk factor for serious problems, including not only Type 2 diabetes but depression.

"It's time for providers to consider the metabolic status of those suffering from mood disorders and vice versa, by assessing mood in patients with metabolic diseases such as obesity and hypertension," Rasgon said. "To prevent depression, physicians should be checking their patients' insulin sensitivity. These tests are readily available in labs around the world, and they're not expensive. In the end, we can mitigate the development of lifelong debilitating diseases."

Rasgon is a member of the Wu Tsai Neurosciences Institute at Stanford, Stanford Cardiovascular Institute, and the Stanford Maternal and Child Health Research Institute.

Other Stanford co-authors of the study are former clinical research coordinator Lexi Nutkiewicz; Julia Simard, ScD, associate professor of epidemiology and population health; and Victor Henderson, MD, professor of epidemiology and population health and of neurology and neurological sciences.

Other researchers from the Amsterdam University Medical Center, as well as a researcher from Rockefeller University, contributed to the work.

Provided by Stanford University Medical Center

Citation: Insulin resistance doubles risk of major depressive disorder, study finds (2021, September 23) retrieved 19 September 2024 from <https://medicalxpress.com/news/2021-09-insulin-resistance-major-depressive-disorder.html>

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