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Are Mood Disorders Actually Metabolic Diseases Rooted in Insulin Resistance?

Analysis by Dr. Joseph Mercola | July 17, 2026

STORY AT-A-GLANCE

- Bipolar disorder and depression affect tens of millions globally, long treated as strictly brain-based illnesses, yet both consistently show high rates of insulin resistance and metabolic disturbances
- A 2025 Nature Neuroscience study found that pancreatic insulin release and hippocampal activity are linked through a circadian feedback loop. This suggests bipolar mood shifts arise from disrupted metabolism, not brain chemistry alone
- Earlier research in 2022 showed lithium stabilizes mood partly by restoring insulin signaling, while a clinical trial found metformin improved both insulin sensitivity and psychiatric symptoms in treatment-resistant bipolar depression patients
- Insulin resistance is extremely widespread, with around 40% of Americans affected, driven by refined sugars, seed oils, stress, sleep loss, and environmental exposures that disrupt the body's natural energy regulation
- Supporting insulin sensitivity involves stepwise changes, replacing damaged fats and ultraprocessed foods, introducing gut-friendly carbs and fibers gradually, managing stress, improving sleep, and staying active to stabilize both metabolic and mental health

Bipolar disorder and depression affect millions of people worldwide. Estimates suggest that more than 37 million people live with bipolar disorder,[1] and close to 4% of the global population experiences major depression.[2] These conditions are almost always

described as brain-based, centered on chemical imbalances, circuitry disruptions, or genetic vulnerabilities, and that view has shaped their treatment for decades.[3]

Another factor that deserves attention is how often these same conditions are accompanied by metabolic disturbances, particularly insulin resistance. The consistent overlap makes it clear that your mental health and your metabolic health are deeply connected, bound together in ways that standard treatment models have rarely recognized.

Researchers have begun to investigate this connection in greater depth.[4] Their work suggests that disturbances in insulin signaling are one of the hidden drivers behind the mood instability seen in bipolar disorder and depression, opening a broader understanding of how disrupted energy regulation manifests as both metabolic disease and psychiatric illness.[5]

What Is the Role of Insulin?

Insulin is one of the body's most important signaling hormones. Its primary job is to help your cells take in glucose, which is the main fuel that keeps them alive and functioning. Without insulin, glucose stays in your blood instead of moving into your tissues, and your cells are left without the energy they need to work properly.[6,7]

- **Insulin is produced by beta cells in the pancreas —** Once released, it travels through your bloodstream and attaches to receptors on the surface of your cells. This connection signals the cells to open specialized channels so glucose can flow inside and fuel the chemical reactions that sustain life. When this process runs smoothly, every organ in your body has access to the energy it requires.

- **After a meal, this system springs into action —** As blood sugar rises from the carbohydrates you eat, your pancreas quickly senses the change and responds by releasing insulin. The hormone acts almost immediately, moving glucose out of the

blood and into your cells, preventing sugar levels from climbing too high. This not only protects you from dangerous spikes in blood sugar but also ensures that your cells have a constant stream of energy to draw upon.

- **Insulin plays a stabilizing role in your body's overall energy —** Although insulin's work happens on a microscopic level, the impact is enormous. From the way your brain processes thoughts to the way your muscles contract during movement, every action depends on insulin's ability to keep energy flowing.

- **Insulin also affects how your body stores and manages that energy —** It signals when to store glucose in your liver and muscles as glycogen, a form of backup fuel you can draw on later when you are active or between meals. It influences how much fat is stored, how muscle tissue is preserved, and even how hungry or full you feel.

  By integrating these signals, insulin makes sure that your energy needs are met not just in the moment but in the hours and days that follow. Its goal is always the same — to match the supply of fuel with the demands of your cells, so your body and brain function without interruption.

Despite the precision of this system, insulin's balance can be disrupted. The effect of this breakdown does not stop at your muscles or liver. It extends to your brain, where neurons also depend on insulin to regulate energy use.

How Insulin Signaling Links the Pancreas to Mood Shifts

Research published in Nature Neuroscience examined how pancreatic function may influence mood regulation in bipolar disorder. The researchers began with pancreatic islets derived from induced pluripotent stem cells (adult cells reprogrammed to develop into many different cell types) taken from individuals with bipolar disorder. These cells showed reduced insulin secretion, linked to abnormally high expression of the gene RORβ, already recognized as a genetic risk factor for the condition.[8]

- **Modeling RORβ effects in mice —** To test how this genetic change influences behavior, researchers engineered mice with RORβ overexpressed specifically in pancreatic β cells. During the light phase, the animals showed depression-like behaviors, while during the dark phase, which is normally their active period, they exhibited mania-like behaviors. This alternating rhythm mirrored the mood swings of bipolar disorder.

- **Suppressed insulin tied to hippocampal hyperactivity —** In the light phase, RORβ overexpression suppressed insulin release from pancreatic islets. This was accompanied by increased hippocampal activity. Since the hippocampus regulates mood, memory, and stress responses, the findings revealed that reduced pancreatic insulin coincided with abnormal hyperactivity in mood-related brain circuits.

- **Carryover effects into the dark phase —** The hippocampal hyperactivity seen during the light phase influenced pancreatic function later in the cycle. By the dark phase, insulin release rebounded to higher-than-normal levels, hippocampal activity dropped, and the mice shifted into mania-like behavior. The study showed how disruptions in one part of the cycle set the stage for opposite changes in the next.

- **Discovery of a circadian feedback loop —** Researchers identified a feedback circuit connecting pancreatic insulin release with hippocampal neuronal activity. Insulin influenced how the hippocampus functioned, and hippocampal activity fed back to alter pancreatic insulin secretion. This loop was governed by circadian rhythms, meaning that time-of-day changes were central to the observed mood fluctuations.

  The findings suggest that the alternating depressive lows and manic highs of bipolar disorder stem from a dysregulated pancreas-hippocampus circuit. Metabolic and mood symptoms represent two sides of the same biological process, linked through circadian feedback.

- **Broader relevance to other conditions —** Although focused on bipolar disorder, the results also apply to conditions where metabolic dysfunction and mood instability appear together, including major depression and schizophrenia. Because RORβ also

regulates circadian timing, the work highlights the therapeutic potential of strategies that align with daily rhythms, such as medication scheduling, light therapy, or dietary timing.

The study reframes bipolar disorder as more than a disorder confined to the brain. By linking a genetic risk factor to disrupted insulin release in the pancreas and to circadian shifts in hippocampal activity, it positions metabolism at the very core of conditions that have long been treated as if they were separate from it.

Earlier Evidence Linking Insulin to Bipolar Disorder

In 2022, researchers began framing bipolar disorder through the lens of metabolism, showing how disrupted insulin signaling might underlie the instability of mood. Two key studies that year pointed to the same conclusion — correcting insulin resistance can restore stability in a condition long defined by treatment resistance.[9,10]

- **A perspective placed insulin resistance at the center of bipolar pathology —** A Translational Psychiatry perspective argued that lithium's therapeutic power could be explained not only by its influence on neurotransmission but also by its ability to restore insulin signaling inside the brain.

  Lithium acts on the PI3K/Akt pathway and its downstream target glycogen synthase kinase 3 (GSK3), which are both central to insulin's role in regulating neuronal energy use. By modulating these pathways, lithium improves glucose uptake in neurons, ensuring they have the energy needed for stable function. This reframed bipolar disorder as a problem of energy dysregulation, not just neurotransmitter imbalance.[11]

- **A proof-of-concept trial tested the metabolic model in patients —** That same year, researchers from the University of Pittsburgh and Dalhousie University conducted a clinical trial with 45 middle-aged patients suffering from treatment-resistant bipolar depression.

On average, participants had been ill for more than 25 years, failed nearly a dozen psychiatric medications, and lived with unremitting symptoms. They were randomized to receive either metformin, a common insulin-sensitizing drug, or a placebo, while continuing their usual psychiatric care.[12]

- **Metformin improved both insulin sensitivity and psychiatric symptoms —** Within weeks, patients receiving metformin began to improve. By 14 weeks, half had regained insulin sensitivity, and this biological change coincided with sharp reductions in depression and anxiety.

  Improvements persisted for up to 26 weeks, marking a dramatic turnaround for individuals who had seen little relief in decades. According to study coauthor Dr. Jessica Gannon:

  > *"Given that the only other therapy that works comparably well is electroconvulsive therapy — a procedure that involves applying electrical current to the patient's brain, causing a controlled seizure — achieving the same result just by restoring insulin sensitivity seems astounding."*[13]

Both of these studies showed that bipolar disorder is deeply tied to impaired insulin signaling, whether in neurons unable to efficiently use glucose or in systemic resistance blunting insulin's effects throughout the body. Correcting these disturbances stabilized mood where traditional psychiatric drugs had failed.

Why Is Insulin Resistance So Alarmingly Common?

In the United States, around 40% of people are insulin-resistant.[14] The reason it is so widespread has much to do with the way you eat, live, and interact with your environment.

- **The type of sugar you consume plays an important role —** When you eat a piece of whole fruit, the natural sugars are packaged with fiber, vitamins, and minerals that slow absorption and ease the demand on your pancreas. But when you drink a soda

or eat candy loaded with refined sugar, there are no such buffers.

Glucose floods into your bloodstream, your blood sugar rises rapidly, and your pancreas responds by releasing large amounts of insulin. When this happens repeatedly, day after day, your cells begin to dull their response to insulin, and resistance takes hold.

- **The kinds of fats you eat also matter —** Seed oils such as soybean and corn oil have become a staple in modern processed foods. These oils are highly unstable, breaking down easily into harmful byproducts, especially when heated.

  Over time, these byproducts damage your cells and interfere with how they respond to insulin. They also change the very makeup of your cell membranes, which disrupts the function of insulin receptors and makes it even harder for your cells to use glucose effectively.

- **Beyond diet, environmental exposures add to the problem —** Certain plastics release chemicals that act as endocrine disruptors, impairing the way your hormones work. Constant exposure to electromagnetic fields (EMFs) from electronic devices has also been shown to influence cellular stress responses. These hidden factors layer onto an already heavy metabolic load, making it even more difficult for your body to keep insulin signaling on track.

- **Lifestyle patterns further push the balance in the wrong direction —** Chronic stress keeps cortisol levels elevated, and cortisol directly reduces your cells' sensitivity to insulin. Poor sleep disrupts the hormones that regulate hunger and blood sugar, making you more likely to crave sugary or starchy foods while also leaving your body less able to handle them.

  Physical inactivity exacerbates these problems. When your muscles are not regularly contracting and using glucose for fuel, the sugar remains in your bloodstream, and your pancreas is forced to release more insulin to try to keep up.

- **All of these factors overlap in ways that strain your metabolism —** They create an environment where insulin is constantly working harder to move glucose into your cells, while your cells are responding less and less. Over time, the result is a system that can no longer keep up, leaving you vulnerable to a cascade of health problems that begin with impaired energy regulation.

Using HOMA-IR to Spot Insulin Resistance Early

One of the most straightforward ways to gauge how well your body responds to insulin is through a test called HOMA-IR, short for Homeostatic Model Assessment of Insulin Resistance.

- **How to get your HOMA-IR score —** Unlike more complex methods, it requires only two basic blood tests, both done first thing in the morning before you eat. One test measures fasting glucose and the other measures fasting insulin. These are widely available, relatively inexpensive, and can be ordered through most laboratories. Once you have those two numbers, they are entered into a simple formula:

HOMA-IR = (Fasting Glucose in mg/dL × Fasting Insulin in μU/mL) ÷ 405

- **This score shows how hard your body is working to keep blood sugar in check —** A higher number means your pancreas is pushing out more insulin to control your glucose levels, which signals that your cells are becoming resistant to insulin's effect. Ideally, your HOMA-IR should be under 1.0. Even values around 1.0 deserve attention, because they show that your body may already be moving toward resistance. The lower the number, the better your insulin sensitivity.

- **One of the reasons HOMA-IR is so useful is its simplicity —** You do not need to schedule multiple appointments or go through complicated testing. You fast overnight, go to the lab for a quick blood draw, and have the results processed soon after. This ease makes it practical not only for scientific research but also for anyone wanting to monitor their metabolic health.

- **The gold-standard but impractical clamp test —** In research, the gold-standard method of measuring insulin sensitivity is the euglycemic hyperinsulinemic clamp. This test involves being connected to intravenous lines for several hours while insulin and glucose are carefully infused, with glucose uptake measured in real time. It is highly accurate but also expensive, time-intensive, and impractical for routine use outside of a research setting.

- **HOMA-IR fills the gap by offering a reliable, accessible alternative —** While no single test can capture the full complexity of your metabolism, this method balances accuracy with practicality. It provides a clear enough signal to identify early shifts toward insulin resistance, long before those changes are visible on standard blood sugar tests.

- **Early detection signals needed lifestyle changes —** Catching insulin resistance early is critical because it allows you to make meaningful changes before more serious problems take root. If your HOMA-IR score rises above 1.0, it is a signal to look more closely at the factors in your daily life that drive resistance — from sugar intake and processed oils to disrupted sleep, chronic stress, and environmental exposures.

The ability to track your progress over time makes HOMA-IR even more valuable. As you make adjustments in diet, movement, and lifestyle, you can retest and see whether your score is improving. That direct feedback provides motivation and clarity, showing you how your efforts translate into measurable improvements in insulin sensitivity and, by extension, in your long-term health.

Steps to Improve Insulin Sensitivity

Reversing insulin resistance is not about quick fixes but about steadily removing the barriers that prevent insulin from doing its job. Because disrupted insulin signaling also affects your brain, these changes support not just your metabolism but also the stability of your mood. Here are strategies I recommend you implement:

- **Start with carbs that are easy on your gut —** Glucose is often automatically viewed as harmful in the context of insulin resistance, yet your body relies on it as a primary fuel. If you cut carbs too low, your body compensates by raising cortisol, a stress hormone that breaks down muscle tissue to make glucose, which weakens your metabolic health over time.

  Most adults require about 250 grams of healthy carbohydrates a day, but if you struggle with bloating, gas, or constipation, jumping straight into high-fiber foods often makes symptoms worse. Starting with gentle sources, such as white rice or whole fruit, gives your cells the glucose they need without overwhelming your gut.

  Once your digestion feels calmer, you will be in a stronger position to add more fiber gradually. Learn more about this in "**The Hidden Triggers of Insulin Resistance and How to Restore Balance**."

- **Introduce resistant starches and root vegetables once stable —** When your system has stabilized, resistant starches and root vegetables can be introduced in small amounts. Cooked and cooled white potatoes or **green bananas** are two reliable starting points.

  If you tolerate these, you can expand to foods like garlic, onions, and leeks, which nourish the bacteria that produce butyrate, a short-chain fatty acid that strengthens your gut lining and supports blood sugar regulation. This is often the stage where people notice steadier energy, fewer cravings, and more balanced glucose levels.

- **As your digestion becomes more resilient, you can slowly rotate in a wider variety of plant foods —** Begin with root vegetables, then move toward leafy greens, beans, legumes, and eventually whole grains. The key is to add them gradually and not to eat the same new food every day at the start. Your gut bacteria need time to adjust to new fiber sources, and pacing yourself helps avoid the discomfort that can come with sudden changes.

Over time, this stepwise approach creates a balanced and diverse fiber intake that stabilizes your metabolism while keeping your gut comfortable. Non-starchy vegetables, starchy roots like sweet potatoes and squash, legumes, and whole grains all contribute to long-term stability, provided you introduce them at a pace your body can handle.

- **Alongside what you add, it is equally important to cut out what damages your gut —** Vegetable oils high in linoleic acid, ultraprocessed foods, and alcohol all erode the gut barrier and encourage the growth of bacteria that worsen inflammation and insulin resistance.

  Replacing these with healthier fats such as grass fed butter, ghee, or tallow helps repair the intestinal lining and supports the balance of your microbiome. A healthier gut environment, in turn, makes your cells more responsive to insulin.

When you take these steps together, you set the stage for real metabolic healing. As your insulin signals strengthen and your energy stabilizes, you also support healthier brain function, reducing the strain that disrupted metabolism places on mood and mental well-being.

Frequently Asked Questions (FAQs) About Insulin Resistance and Mental Health

Q: How exactly does insulin resistance affect my brain?

A: Your brain has insulin receptors, especially in areas that control mood, memory, and stress. When your cells stop responding to insulin, neurons can't take up glucose efficiently. That energy shortage disrupts brain circuits and contributes to mood instability.

Q: If I have depression or bipolar disorder, does that mean I also have insulin resistance?

A: Not always, but the overlap is high. Many people with mood disorders also show signs of insulin resistance, even before diabetes develops. Testing your insulin sensitivity helps you see whether metabolism is contributing to your symptoms.

Q: Does improving insulin resistance really change mood symptoms?

A: Clinical trials show that when insulin sensitivity is restored, patients often experience major improvements in depression and anxiety. In some cases, the effect has been as strong as electroconvulsive therapy, but achieved simply by correcting metabolism.

Q: Can changing my diet really affect my mood?

A: Yes. What you eat influences insulin signaling, and insulin affects both your energy metabolism and your brain. Choosing whole-food carbohydrates, resistant starches, and healthy fats, while cutting seed oils and ultraprocessed foods, helps restore insulin sensitivity and improve mood stability.

Q: What lifestyle habits matter most for improving insulin sensitivity?

A: Beyond diet, daily movement, good sleep, and managing stress are important. Muscles that move use up glucose, lowering the demand for insulin. Quality sleep restores your hormones, and stress reduction lowers cortisol, which otherwise blunts insulin's effects.

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