

Researchers look at genetic clues to depression in more than 14,000 people

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The core experiences of [depression](#)—changes in energy, activity, thinking and mood—have been described for more than 10,000 years. The word "depression" has been used for about 350 years.

Given this long history, it may surprise you that experts [don't agree](#) about what [depression](#) is, how to define it or what causes it.

But many experts do agree that depression [is not one thing](#). It's a large family of illnesses with different causes and mechanisms. This makes choosing the [best treatment](#) for each person challenging.

Reactive vs. endogenous depression

One strategy is to search for [sub-types of depression](#) and see whether they might do better with different kinds of treatments. One example is contrasting "reactive" depression with "endogenous" depression.

Reactive depression (also thought of as social or psychological depression) is presented as being triggered by exposure to stressful life events. These might be being assaulted or losing a loved one—an understandable reaction to an outside trigger.

Endogenous depression (also thought of as biological or genetic depression) is proposed to be caused by something inside, such as genes or brain chemistry.

Many people working clinically in mental health [accept](#) this sub-typing. You might have read about this [online](#).

But we think this approach is way too simple.

While stressful life events and genes may, individually, contribute to causing depression, they also interact to [increase the risk](#) of someone developing depression. And evidence shows that there is a [genetic component](#) to being exposed to stressors. Some genes affect things such as personality. Some affect how we interact with our environments.

What we did and what we found

Our team set out to look at the role of genes and stressors to see if classifying depression as reactive or endogenous was valid.

In the [Australian Genetics of Depression Study](#), published in *Molecular Psychiatry*, people with depression answered surveys about exposure to stressful life events. We analyzed DNA from their saliva samples to calculate their genetic risk for [mental disorders](#).

Our question was simple. Does genetic risk for depression, [bipolar disorder](#), schizophrenia, ADHD, anxiety and neuroticism (a personality trait) influence people's reported exposure to stressful life events?

You may be wondering why we bothered calculating the genetic risk for mental disorders in people who already have depression. Every person has genetic variants linked to mental disorders. Some people have more, some less. Even people who already have depression might have a low genetic risk for it. These people may have developed their particular depression from some other constellation of causes.

We looked at the genetic risk of conditions other than depression for a couple of reasons. First, genetic variants linked to depression overlap with those linked to other mental disorders. Second, two people with depression may have completely different genetic variants. So we wanted to cast a wide net to look at a wider spectrum of genetic variants linked to mental disorders.

If reactive and endogenous depression sub-types are valid, we'd expect people with a lower [genetic component](#) to their depression (the reactive group) would report more stressful life events. And we'd expect those with a higher genetic component (the endogenous group) would report fewer stressful life events.

But after studying more than 14,000 people with depression we found the opposite.

We found people at higher genetic risk for depression, anxiety, ADHD or schizophrenia say they've been exposed to [more stressors](#).

Assault with a weapon, [sexual assault](#), accidents, legal and financial troubles, and [childhood abuse](#) and neglect, were all more common in people with a higher genetic risk of depression, anxiety, ADHD or schizophrenia.

These associations were not strongly influenced by people's age, sex or relationships with family. We didn't look at other factors that may influence these associations, such as socioeconomic status. We also relied on people's memory of past events, which may not be accurate.

How do genes play a role?

Genetic risk for mental disorders changes people's sensitivity to the environment.

Imagine two people, one with a high genetic risk for depression, one with a low risk. They both lose their jobs. The genetically vulnerable person experiences the job loss as a threat to their self-worth and social status. There is a sense of shame and despair. They can't bring themselves to look for another job for fear of losing it too. For the other, the job loss feels less about them and more about the company. These two people internalize the event differently and remember it differently.

Genetic risk for mental disorders also might make it more likely people find themselves in environments where bad things happen. For example, a higher genetic risk for depression might affect self-worth, making people more likely to get into dysfunctional relationships which then go

badly.

What does our study mean for depression?

First, it confirms genes and environments are not independent. Genes influence the environments we end up in, and what then happens. Genes also influence how we react to those events.

Second, our study doesn't support a distinction between reactive and endogenous depression. Genes and environments have a complex interplay. Most cases of depression [are a mix](#) of genetics, biology and stressors.

Third, people with depression who appear to have a stronger genetic component to their depression report their lives are punctuated by more serious stressors.

So clinically, people with higher genetic vulnerability might benefit from learning specific techniques to manage their stress. This might help some people reduce their chance of developing depression in the first place. It might also help some people with depression reduce their ongoing exposure to stressors.

More information: Jacob J. Crouse et al, Patterns of stressful life events and polygenic scores for five mental disorders and neuroticism among adults with depression, *Molecular Psychiatry* (2024). [DOI: 10.1038/s41380-024-02492-x](https://doi.org/10.1038/s41380-024-02492-x)

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