



Research in Context: Obesity and Metabolic Health

Losing weight and reversing obesity might seem straightforward: Eat fewer calories than you burn. But that's not as easy as it sounds.

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Obesity has been a growing problem in the U.S. More than 40% of adults and 19% of children now have obesity. Some people may think of obesity as a consequence of lifestyle choices. But there are many factors affecting body weight that are beyond our conscious control. Researchers are only beginning to understand them.

The rise in obesity has serious implications. Excess body fat can trigger inflammation, high blood sugar, and high blood pressure. Levels of fat and cholesterol in the blood increase, raising the risk of heart disease and stroke. Fat can also get stored in places it normally wouldn't be, such as the liver and kidneys.

Obesity and some of its associated symptoms, such as high blood pressure and high blood sugar, contribute to a condition known as metabolic syndrome. People with metabolic syndrome have a higher risk of developing many chronic diseases, including type 2 diabetes, cardiovascular disease, and even certain cancers.

National Institutes of Health (NIH)-funded researchers have been working for a deeper understanding of metabolic health. They are trying to learn how our bodies regulate how many calories we take in and burn, and how our behavior and environment can promote obesity. Research has also led to a more nuanced understanding of fat itself. This research may result in better ways to prevent and treat metabolic syndrome.

Body Weight, Diet, and Appetite

Losing weight and reversing obesity might seem straightforward: eat fewer calories than you burn. But many of us know that's not as easy as it sounds.

"I think that most people overestimate how much conscious control we have, over long periods of time, over both the amount of food that we eat as well as the type of food that we eat," says NIH metabolism researcher Dr. Kevin Hall.

If you cut down how many calories you eat and do more physical activity, you will begin to lose

weight. But as you do so, your body adjusts. You start burning fewer calories, so the calorie deficit shrinks. Your appetite may also go up, driving you to eat more. Both of these changes happen on an unconscious level. So, failure to lose a substantial amount of weight through diet and exercise can't just be blamed on a lack of willpower. There's a fundamental biological drive that has to be overcome.

"People perceive hunger in their brain," explains Dr. Aaron Cypess, another NIH metabolism researcher. "And if the brain is not getting the right amount of signal saying that there's enough calories, then the brain will lead one to eat more." Research on the recently approved weight-loss drugs semaglutide (Wegovy) and liraglutide (Saxenda) supports this view. These drugs work by targeting areas of the brain that regulate appetite.

But researchers have also discovered that the foods available to us are not created equal when it comes to appetite control. Hall's research has found that people unconsciously eat more calories' worth of certain foods than others. In one study, 20 people stayed at the NIH Clinical Center's Metabolic Clinical Research Unit for four weeks. They were told they could eat as much or as little as they wanted. Each participant was given a diet that was low in fat and high in carbohydrates for two weeks and one that was low in carbohydrates and high in fat for two weeks. Both diets were based on minimally processed foods.

The participants reported no differences in hunger, satisfaction, or fullness between the diets. But when provided with the low-fat diet, they ended up eating almost 700 calories less per day than when given the low-carb diet. They also lost more body fat. Participants still lost weight on both diets, suggesting that both of these restricted food patterns caused people to eat fewer calories than their habitual diets, at least in the short term.

Food processing may also play a role in food intake. Hall's team tested two food patterns with the same number of calories, salt, sugar, fat, fiber, and carbohydrates. But one diet was high in minimally processed foods while the other was high in "ultra-processed" foods. These are ready-to-heat or ready-to-eat foods that have undergone extensive industrial processing. They have additives and other ingredients not typically used in home cooking. For example, those on the ultra-processed diet received a bagel and cream cheese with turkey bacon for breakfast one day. Those on the unprocessed diet received oatmeal with walnuts, bananas, and coconut.

As in the first study, participants reported no differences in hunger, fullness, or satisfaction between the diets. But during the ultra-processed dietary period, participants ate about 500 calories more per day than during the unprocessed period. The ultra-processed foods caused participants to gain an average of 2 pounds of weight, much of it from increased body fat. When participants were exposed to the unprocessed diet, they lost weight and body fat. This finding suggests that the increasing amount of ultra-processed foods in our environment may have helped to drive the rise in obesity.

Hall's group is now trying to figure out what it is about ultra-processed foods that leads people to eat more calories, and how this happens. He notes that getting rid of ultra-processed foods

entirely wouldn't be practical. "We're not going to go from a country where half of the food supply is ultra-processed foods to a country where a very small fraction of the food supply is ultra-processed foods. We rely on them too much. I rely on them still. They're tasty, they're convenient, and it doesn't take much time or effort or skill to prepare them."

But understanding what makes these foods problematic could lead to healthier eating. Manufacturers might be able to reformulate ultra-processed foods to be less likely to cause overeating. Consumers could learn what products to avoid. And government regulators could craft policies to help improve people's metabolic health.

Sleep and Metabolic Health

Diet and exercise aren't the only activities that affect your metabolic health. Our metabolism, like many aspects of our biology, varies with the time of day. So besides what you eat, when you eat can affect your body and your health.

Research has found that sleep has a major effect on the body's metabolism. Experts recommend that adults get at least seven hours of sleep each night. Yet many American adults regularly get less than that—and some aren't able to get all their sleep at night.

Poor sleep is linked to the risk of obesity and diabetes. Our bodies are most capable of taking in nutrients during the daytime when we're awake. People who spend too much time awake end up eating more—particularly at night, when their bodies aren't ready for it. Eating at night tends to lead to more energy being stored as fat. This is particularly a problem for night shift workers, who have an increased risk of metabolic disorders. Not getting enough sleep also impairs the body's ability to respond to insulin, the hormone your body uses to regulate blood sugar. Over time, impaired insulin sensitivity can lead to type 2 diabetes.

Some people try to sleep longer on the weekends to make up for the sleep they didn't get during the work week. But a recent NIH-funded study suggests that this "catch-up" sleep can't counteract the effects of sleep deprivation. People who were limited to five hours of sleep per night ate more after-dinner snacks than those allowed to sleep normally. During the two-week study, they gained about 3 pounds on average, and their insulin sensitivity declined.

After five days, some of the sleep-deprived participants were allowed two days of unrestricted sleep. But this barely helped. They fell far short of making up for the more than 12 hours they lost during the preceding five days. After-dinner snacking decreased during the two-day recovery period, but it went back up upon returning to restricted sleep. In the end, they didn't gain any less weight than people who didn't get weekend recovery sleep, and their insulin sensitivity decreased even more.

"In the case of smoking, we wouldn't say, 'oh, you can smoke for five days, just take the weekend off, and it'll be okay,'" explains study leader Dr. Kenneth Wright, Jr. of the University of Colorado Boulder. "We're not trying to say, don't sleep in on the weekend. We're trying to say get adequate sleep as much as you can on a consistent basis."

Limiting the times you eat through brief intentional periods of fasting may also have benefits for metabolic health. Studies in animals have found that repeated cycles of fasting, even without reducing total calories, can improve a range of metabolic and immune functions. Examples include lower cholesterol levels, blood pressure, and inflammation.

Small clinical studies have also found that periodic fasting can have health benefits in people. Some of the benefits seen include lower inflammation and blood pressure, and better control of blood sugar. Researchers are now studying whether such approaches might be safely used to improve human health over the long term, and whom they might benefit.

Different Kinds of Fat

Researchers have discovered that it isn't only how much fat you have that matters; it's the kind of fat. The human body contains two main kinds. Most is white fat. This stores excess energy in the form of molecules called triglycerides. White fat is found throughout the body, usually in a layer under the skin and around internal organs. Having too much white fat is what makes someone have obesity.

But there's another kind of fat, called brown fat. Its job is to help maintain body temperature by burning triglycerides to generate heat. Until about 15 years ago, humans were believed to lose most of their brown fat after infancy. It was thought that any brown fat that remained in adults didn't serve any function. Since then, researchers have learned that nearly every adult human has some functioning brown fat. It's found only in certain places in people: the neck and shoulders, along the spine, and around the kidneys.

Brown fat may have a big impact on our metabolic health. In mice, activating brown fat reduces levels of triglycerides and cholesterol in the blood. It also prevents atherosclerosis, a sticky buildup along the artery walls that contributes to heart disease. In people, more brown fat is associated with lower rates of type 2 diabetes, cardiovascular disease, high blood pressure, and heart failure. So, having more brown fat, or more active brown fat, may be good for metabolic health. This suggests that increasing brown fat activity might protect against metabolic syndrome.

The simplest way to activate brown fat is long exposure to cold temperatures. But people might not be willing to spend hours a day sitting in the cold. It would be more practical if we could take a drug to activate our brown fat.

Cypess and his team are studying one potential drug, mirabegron, that is currently approved by the Food and Drug Administration for treating overactive bladder. It works by binding to and activating a protein found on the surface of certain cells, including brown fat cells.

In a small trial, Cypess and his team showed that mirabegron could activate brown fat at least as well as cold exposure. In a follow-up study, mirabegron increased the amount and activity of brown fat over the course of the study. The amount of energy used increased, and some measures of metabolism improved, although there were no changes in body weight or the percentage of body fat.

These changes were comparable to those caused by mild exercise, bariatric surgery, or anti-diabetic drugs. The only side effect was a small increase in resting heart rate. This is a known side effect of mirabegron and was not large enough to put the participants' safety at risk.

Cypess's team now seeks to figure out how brown fat activation leads to these metabolic changes. They're also looking at whether mirabegron can help people at risk for metabolic disease.

"This field is interesting, because there are a lot of people with very strong opinions who will tell you that they already know the answers," Hall says. "It seems to me that there are still a lot of really important open questions. We're getting closer to understanding why obesity has increased. We thankfully have some seemingly effective ways to deal with people who have severe obesity, or complications of obesity. But there's still a lot of work to do."

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