Grow fat, get thin? We put brown fat to the test

by Chloe Lambert

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GIVEN my predilection for peanut butter and ice cream, the offer of a scan to measure my body fat wouldn't normally fill me with excitement. But this is no ordinary fat map, and for once I'm hoping to have a lot of the stuff.

While normal white fat stubbornly stores excess calories on hips, bellies and thighs, over the last few years a picture has emerged of a different kind of fat – one which, paradoxically, might help us to lose weight. This is brown fat, which challenges all our assumptions about the fat in our bodies: it burns calories rather than storing them.

It was only six years ago we discovered that brown fat exists and is active in adults. Since then, it has become the focus of attention as a potential tool to help combat obesity and its related diseases. And the idea that there might be a way to burn through calories without the need to exercise is a tempting prospect for many of us.

"We all know you only need a modest change in energy balance to put on weight – eating one or two extra biscuits a day is enough," says Michael Symonds at the University of Nottingham, UK. "So if you could activate brown fat, or increase its activity, you could potentially reduce your body weight."

Symonds is one of a number of researchers working to develop behavioural, surgical and pharmaceutical therapies that might harness the power of brown fat, and some of these could be as simple as taking a cold dip in the pool or eating spicy food. So when the offer came to work with his team to try and give my own brown fat a boost, I had to give it a try.

What makes brown fat so interesting is its ability to burn food directly to produce heat, whereas energy extracted from food is usually stored first, then released during activity such as exercise. It can produce 300 times more heat per gram than any other tissue in the body. This is because brown fat cells have a disproportionately high number of mitochondria – the small energy producing structures in cells – which also gives the stuff its eponymous colour. These mitochondria are slightly different from those in other cells, too, because they contain a protein called thermogenin, or UCP1, which enables brown fat to turn energy to heat directly.

"Brown fat can produce 300 times more heat per gram than any other tissue in the body"

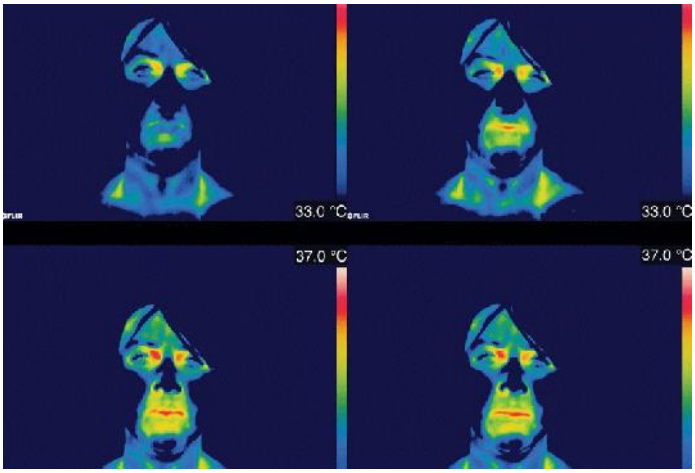
This furnace-like ability is vital for regulating temperature in some mammals and in babies, who are unable to shiver to keep warm. But until recently it was thought to become defunct after infancy in humans. Then in 2009, several studies showed that brown fat was present and functional in adults in the neck, shoulders and around the spinal cord.

This discovery changed the question from whether adults have brown fat, to whether we can make use of it to help with weight control. "It was a eureka moment," says Symonds.

Although I'm not overweight, the idea of a fat that makes me thinner is certainly tantalising. The amount of brown fat each of us has varies, though. Slimmer people tend to have more of it, which might help explain why some people seem to burn through everything they eat, while others pile on the pounds.

So the first step is to find out how much, if any, of this "good" fat I have. Because brown fat is activated when the body is exposed to the cold, Symonds and his team have helped pioneer the use of a thermal imaging camera to detect it. The images clearly show two small glowing triangles at the base of my neck – hotspots of brown fat that get brighter when I plunge my hand in a bucket of cold water and the cells set to work (see image next page).

Because I have brown fat, Symonds says my best bet to try and burn calories the lazy way is to expose myself to the cold. When animals are cold, they initially regulate their temperature by shivering. But after repeated exposure, shivering decreases while energy expenditure stays the same. Studies in rodents have shown that this is down to brown fat activity. If the same is true in humans, then regular cold exposure could help you adapt to the cold and burn calories in the process.



Clockwise from top: Brown fat glows brighter as it becomes more active with time after submerging a hand in cold water *(Image: Michael Symonds)*

Evidence for this comes from an intriguing study conducted by the US army in the 1960s, which subjected 10 almost nude men to temperatures of 11º C, for 8 hours a day for a month. Electrodes on their skin showed that, like rats, shivering decreased after about two weeks, suggesting that their bodies had somehow adapted to the cold. The team concluded that another metabolic process was at work, although it remained a mystery.

Fifty years later, Anouk van der Lans at Maastricht University in the Netherlands and colleagues wondered whether brown fat was responsible. So in 2012 they recreated the study using PET scans and fat and muscle biopsies to measure brown fat activity, as well as monitoring shivering. After 10 days, brown fat activity had increased and the subjects were better at producing heat without shivering, so they shivered less. They also found the cold easier to tolerate.

Encouragingly, in this study, a temperature of about 16º C was cold enough to switch on the tissue. “Nobody thinks that getting so cold that you’re uncomfortable is necessary,” says Aaron Cypess of the US National Institute of Diabetes and Digestive and Kidney Diseases, an author of one of the 2009 papers.

But with just five days until my follow-up scan, Symonds says it won’t hurt to get temperatures lower than that. So I keep the central heating at home off or on a low setting, even though it’s just 4º C outside. I drink iced water throughout the day, have a cool shower every morning and, for good measure, go for a swim in my local outdoor pool where the water is a breathtaking 3º C.

How many calories can I expect to shed? Estimates vary hugely. One trial of Japanese men found that spending 2 hours a day in a 17º C room for six weeks boosted brown fat activity by 50 per cent, and got rid of 5 per cent of their body fat. At the start of the experiment the men burned 108 calories during 2 hours in the cold, but this rose to 289 calories after doing it every day for six weeks.

That doesn’t necessarily mean all those calories are burned by the brown fat itself – in studies that only involve short bursts of cold exposure, it could be down to other mechanisms like shivering. For example, one study of volunteers with an average of 50 grams of brown fat found they burned around 300 extra calories a day when exposed to moderate cold for 30 minutes – but brown fat only accounted for 20 calories of this.

Despite the mixed results, those figures are encouraging enough for some people to make cold exposure part of their daily routine. “The mechanism of how it happens is important to understand, but for practical reasons, the result is what people care about,” says Wayne Hayes, a NASA scientist who has created the Cold Shoulder, a waistcoat filled with ice packs designed to activate brown fat.

Cypess and others believe that brown fat could make a contribution to weight loss strategies with regular cold exposure. But what if you don’t like the cold? There could be a tastier alternative.

Beige is the new white

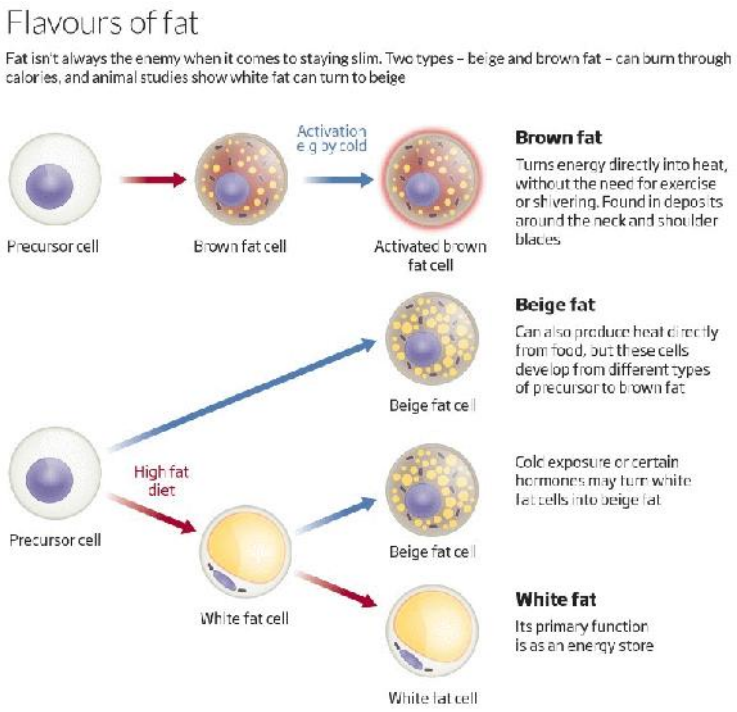
Capsaicin, a compound in chillies, seems to stimulate brown fat in a similar way. Mice fed capsaicin as part of a high-fat diet, for example, have increased metabolic activity and don't put on weight. This fits with a small study in which 10 men who took capsaicin pills daily had greater brown fat activity in the cold and burned more calories after six weeks.

"Capsaicin is promising as it is natural, and relatively safe and inexpensive," says Cypess. "But we are awaiting the definitive experiment showing that a dose of capsaicin directly leads to activation of brown fat."

In the meantime, brown fat could have other benefits aside from calorie burning. It releases hormones that help regulate the metabolism of glucose and fatty acids, so might be useful to help treat diabetes and fatty liver disease. Humans and other animals with high brown fat levels have been shown to have better blood sugar and insulin regulation.

But there is a hitch: we have paltry amounts of brown fat and obese people have especially low levels. Stores also deplete as we age.

For that reason, arguably the biggest recent breakthrough in the field has been the identification of a third kind of fat, called beige fat. First described by Bruce Spiegelman at Harvard Medical School in 2012, beige fat has a different origin to classical brown fat, but it contains the same all-important protein, UCP1, which burns calories to generate heat. And while brown fat forms in tight pockets, beige fat is dispersed in white fat cells. Even better, it might be possible to transform white fat into the calorie-burning beige variety (see "Flavours of fat" at right).

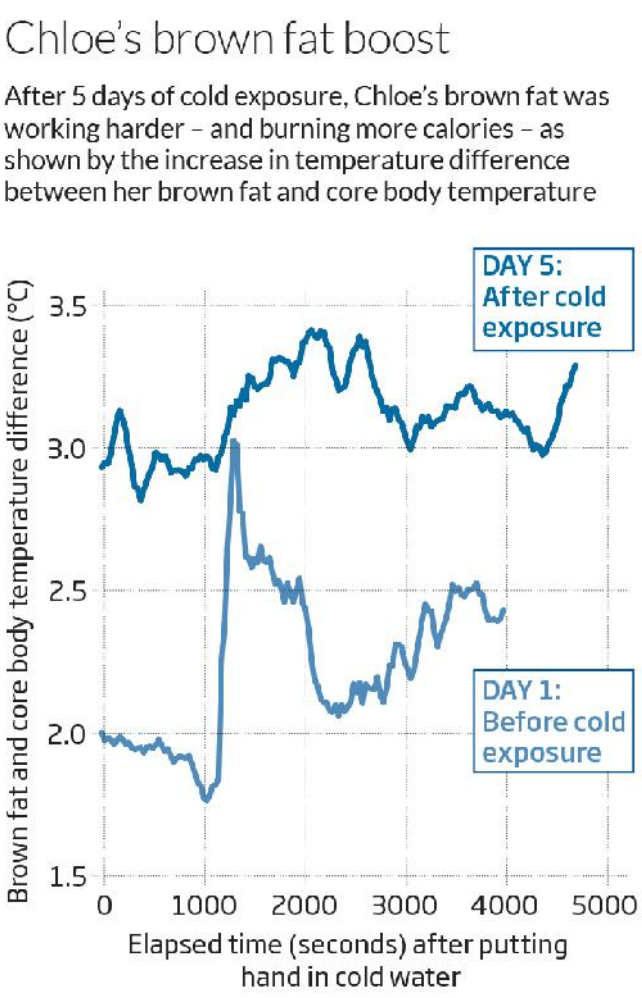


"With most experiments on brown fat you don't induce much new tissue, you just activate it," says Ronald Kahn at the Joslin Diabetes Center in Boston. "With beige fat you get both an increase in the activity, and in the amount. So this is where people believe there are big therapeutic opportunities."

While most research has so far been in rodents, there is tentative evidence that humans too can turn white fat to beige. One way could be to throw off the duvet. Men who slept in 19º C bedrooms with only bed sheets had 42 per cent more brown fat after four weeks, found Francesco Celi at Virginia Commonwealth University and colleagues. Glucose uptake increased in white fat, suggesting a rise in beige fat cells nestled within it. The men's insulin resistance, which is a key issue in diabetes, also improved.

Exercise might also help convert cells. Celi has found hints that a hormone called irisin, produced when muscles contract, stimulates white fat to produce beige fat cells, although the findings are still being debated. For good measure, I keep up my exercise routine, but switch indoor aerobics for a jog in the cold.

When I return to the lab after five days, Symonds's team finds that the difference between my core body temperature and my brown fat temperature had increased (see graph). "That indicates that the brown fat tissue was more active, and having to produce more heat to keep you at a favourable temperature," Symonds says.



Then came the bad news: the brown fat boost didn't translate into any weight loss – in fact, I gained a kilogram. Symonds says it may be that brown fat needs to be activated for a longer period to see a change in fat mass. And although I tried to follow my normal diet, he suspects I may have compensated for the cold by eating more. In the sleep study, the boost in brown fat was reversed after the men spent another month sleeping in a warm room, which suggests you'd need to make cold exposure a long-term fixture.

Third pillar of weight loss

This highlights a big problem with thinking that boosting brown fat with cold exposure is an easy option: to some people, feeling cold is about as unappealing as slogging it out in the gym or living off salad. And our natural response to cold is often to eat more.

So a better tactic might be to find easier ways to simulate these effects. One hope is mirabegron, a drug developed as a treatment for an overactive bladder that also stimulates receptors on the surface of brown fat cells. In January, a team led by Cypess found an increase in brown fat activity in 12 volunteers after they were given a dose of mirabegron. Their resting metabolic rate increased by 203 calories a day. And it works on brown and white fat. "Mirabegron causes white fat stores to break down, likely to be consumed as fuel by brown fat and other organs," says Cypess.

Another approach might be to convert white fat to brown in the lab and then re-insert it into the body. In 2010, Yu-Hua Tseng at Harvard's Joslin Diabetes Center took fat precursor cells from muscle and white fat tissue in mice and exposed them to proteins that influence development into brown fat cells. When they then injected them back into the mice, the treated cells developed into brown fat. Tseng's team has now identified the same mechanism in human fat cells.

A drug that mimics the effects of cold may not be far away either. A team at the University of California has discovered that in cold conditions the body sends signals to immune cells called macrophages, which trigger browning of white fat to generate heat. Injecting mice with a dose of these signalling molecules activated the same immune response without the need to get cold, and the mice started burning 10 per cent more energy.

Combining such approaches with cold exposure could increase brown fat's impact. It's likely that brown fat will become the third pillar of weight loss advice, says Cypess. "When you go to your physician, they'll advise you on eating right, exercising and keeping your brown fat healthy," he says. "And my hope is that if a person is uninterested in cold exposure they will be able to take a drug."

Until then, brown fat might not be the magic bullet so many hope. But it could be extremely effective for weight loss if used in combination with reducing calorie intake, says Kahn. Even a conservative estimate of burning an extra 100 calories a day would equate to losing around half a kilogram a month.

And with developments in thermal technology to monitor brown fat, Symonds is optimistic that screening for it could become routine. “It could provide an index of your metabolic health and tell you whether you are at risk of weight gain,” he says.

As for me, the confirmation that I have brown fat, and can manipulate it, has been reassuring and I’ll certainly be turning the thermostat down a few degrees in the winter. All the same, I won’t be rushing back for another ice cold swim.

When good fat turns bad

Switching on brown fat might help people to slim down (see main story), but switching it off could also be useful. Half of all people with cancer get cachexia, a condition causing extreme thinness, which also accounts for 20 per cent of all deaths from cancer. It now seems that brown fat is involved. Cancerous tumours cause white fat cells to turn into calorie-burning beige fat in mice. If the same is true in people with cachexia, it would explain why they lose weight even if they eat more. Last year, a team at Harvard Medical School identified the protein that tumours release to cause this effect. When mice were treated with an antibody that neutralised the protein, their muscle mass and function were preserved. A similar antibody that works in humans is now being developed, and trials could begin within two years.

Fat FAQ: 9 answers to your burning questions

1. **How quickly does eating too much cause new fat cells to form?**

   “Incredibly fast,” says Matthew Rodeheffer, who studies obesity at Yale University, on the basis of recent research his team conducted on mice. After just five days on a high fat diet, new fat cells had appeared. In humans the process could be even faster, he says, potentially within a day. Once the cells are present, though, it takes them several weeks to actually fill up with fat.

   But Giles Yeo at the University of Cambridge Metabolic Research Laboratories says having more fat cells isn’t necessarily a bad thing. Being able to spread your fat over a larger number of cells means they are less likely to overfill, so you can store more fat while staying metabolically healthy. “Imagine each fat cell is like a balloon, but there is a safe limit to how much fat it can store,” Yeo says. “When they are full, the fat goes to the liver and muscle. It’s one of the key causes of metabolic disorders like diabetes, and heart disease.”

2. **If you have more fat cells, do you put on weight more quickly?**

   “That’s the logical assumption,” says Rodeheffer. “People who have been obese struggle to maintain weight loss. And we think this is probably a major contributing factor.”

   In fact, between 75 and 95 per cent people who lose weight regain most of it within a few years. Part of the problem seems to be the way fat cells communicate with the brain. As well as passively storing fat, these cells send information – usually via hormones – about the level of fat stores in the body, and the body’s metabolic needs. One of these hormones, leptin, signals satiety. In basic terms, if you have a lot of leptin circulating, you feel more full and probably eat less.

But obese and overweight individuals often become leptin-resistant – they have very high levels of it, but it doesn't work, says Rodeheffer. There's a short circuit in their satiety system, and having a certain amount of fat is what causes it.

3. **Is it true that you can never get rid of fat cells – they just grow or shrink?**

   Yes, says Rodeheffer. "All the data basically says that once you gain more fat cells you can't lose them." So when people become overweight it is principally because their existing fat cells have got bigger, although they also produce additional fat cells. When people lose weight the cells shrink, but their number remains the same.

   Fat cells, like all cells in the body, get replaced continuously, but the turnover rate is the same whether people are obese or lean. It's just that your body maintains a larger number of cells if you are or have been obese, Rodeheffer says.

   The exception might be brown fat. Animal studies, and tentative findings in humans, suggest that white fat cells can be turned into a type of brown fat called beige fat. These cells burn, rather than store, energy from food, so might help people manage their weight.

4. **Why do people who have lost weight have trouble keeping it off?**

   There is evidence that overweight people who manage to lose weight, especially serial dieters, put on more weight over time than people who don't diet. Putting on weight and then losing it again seems to cause long-term metabolic changes, and they have to work harder to keep the weight off.

   Yeo thinks that this comes down to changes in the brain rather than the number of fat cells. We have evolved to hold on to fat, he says, so if you lose weight, causing a drop in leptin production, the brain will try and do what it can to bring that weight back up again. "The way it does this is by trying to reduce energy expenditure and increase food intake." The result is that when you compare two people who weigh the same, one of whom has just lost ten kilos, you will find that the newly lighter individual is hungrier and has a slower metabolism than the other person. Research at Columbia University in New York has shown that replacing the leptin reverses these metabolic effects, an idea that could be the focus of drug development to help people keep weight off.

5. **Does eating fat make you fatter than eating other foods?**

   The jury is still out on this one. Not all calories are equal, says Rodeheffer. Eating more calories as fat while maintaining the same overall energy intake makes you store more off the stuff. In animal studies, mice fed a high-fat diet became obese, whether another group fed less fat but the same number of calories did not, he says.

   When it comes to humans, though, evidence is lacking as, for obvious reasons, almost all studies look at people who are already obese. Besides, some fat is crucial in everyone's diet. And because fatty food does make you feel full, some studies suggest that eating full-fat versions of foods such as yogurt results in people eating less overall.

6. **How can being overweight lead to diabetes?**

   Current thinking is that when extra-large fat cells die, cells called macrophages that are involved in the body's general immune response, inflammation, are deployed to engulf the lipid that fills the fat cells. Slice through fat tissue from a person with obesity and some cells will be surrounded by a ring, or "crown", of macrophages – which aren't implicated in normal fat cell turnover.

   We know that inflammation is a huge component of metabolic disease, says Rodeheffer, so this helps explain the link between obesity and metabolic diseases such as diabetes.

7. **Why is it better to be pear-shaped than apple-shaped?**

   There's plenty of evidence that people who store fat on their hips and bottoms are at a lower risk of metabolic and cardiovascular diseases than those who store it around their middle.

   People used to think it was a "geographical" issue, says Yeo – that what mattered was how close the fat is to your organs, and that when fat cells become full, it might leak into the blood vessels surrounding these organs.

   But research is emerging, he says, to show it's really about types of fat. Visceral fat, the kind that builds up around your middle, and which affects men more than women, produces different hormones to subcutaneous fat – found around buttocks and thighs. The evidence for this comes from mice. "When you remove the unhealthy fat from around the organs, and give the mouse a booty – put it on the backside where it's supposed to be fine – the mice are still metabolically unhealthy," Yeo says.

   Visceral fat hormones signal to liver, heart and other organs to make them more resistant to the effects of insulin. And as the cells stretch and grow, they also tear a little, triggering the macrophage immune response again.

8. **Does exercising at low intensities burn more fat?**

   The thinking goes that to burn the most fat during exercise, it's best to stick to lower intensities at which fat, rather than carbohydrate, is used as the main energy source. "Most people would agree that if you exercise at a low intensity, or even at rest, fat is the main fuel source," says Chris Easton, at the University of the West of Scotland, in Paisley, UK. But that can be misleading. For a start, if you're exercising to lose weight, the most important thing is a calorie deficit, and you'll burn more calories faster with more intense exercise.

   Also, the ideal fat burning zone is different for everyone. There is evidence suggesting that the amount of fat you burn rises until about 55 per cent of your maximum heart rate, Easton says. "That's physically demanding – it's not a walk in the park." And it's not 55 per cent for everyone. "Sometimes it's very low in people who are sedentary or obese – they will burn the most amount of fat at lower intensities." Those differences cause confusion. Besides, Easton says, there's a problem with thinking about exercise just in terms of weight loss – doing more intense exercise will boost your physical fitness, and that's where most of the benefits come in. And even in terms of burning fat, the more exercise you do, and the fitter you get, the better you become at burning fat while you exercise. "Untrained and sedentary individuals, following a period of exercise training, use more fat during exercise," Easton says.

9. **Does exercising first thing in the morning burn more fat than exercising later in the day?**

   "The theoretical principle is sound," says Easton. In a fasted state, you have less access to carbohydrate so will use fat as an energy source. Easton, who works with elite athletes, has found that forcing the body to use fat as a fuel in this way is effective even for lean athletes wishing to slim down – for instance boxers and jockeys. "Exercising in the fasted state makes sense for them," he says. Other research shows that intense exercise before breakfast burns more fat and leads to better insulin sensitivity than eating breakfast first and consuming energy drinks throughout – even if the overall calorie intake is kept the same.

   But what about the rest of us? "For normal people, it's probably not going to make much difference," says Easton. "We're not sure yet." If you're only doing a gentle workout, you might still have enough glucose in your blood and glycogen in muscles and liver to fuel the exercise without drawing on fat stores. And if you're running on empty, you may fatigue sooner and work out less than you would with a bit more available energy.