- Obesity

Health

Obesity may come in 11 types

Understanding different forms of obesity could help guide which treatments and prevention strategies work best for individuals, finds **Chris Simms**

IT TURNS out that obesity may be much more complicated than we thought, with the condition potentially existing in up to 11 forms, each caused by distinct biological pathways.

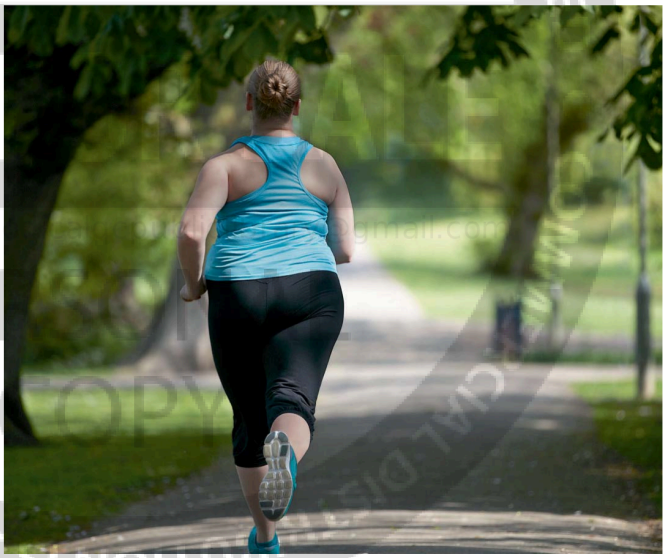
"It's not just about the body mass index or the body appearance; it's more about the biology behind it and how that is related to risk factors," says Akl Fahed at the Broad Institute in Cambridge, Massachusetts.

The World Health Organization defines obesity as having excess fat that poses a risk to health. Whether someone has it is worked out by calculating their body mass index (BMI), a measure of weight relative to height.

As not everyone with obesity has health complications, some researchers have recently suggested introducing a category of "preclinical" obesity. This splits people with the condition into two groups: those with symptoms caused by excess fat, such as breathing difficulties and heart problems, and those who don't have symptoms, but may at a later date. However, these two categories might not be going nearly far enough, according to work by Fahed and his colleagues.

The researchers did a genome-wide association study on more than 2 million people with obesity, with ancestries from all over the world, in which they looked for links between genes and BMI, as well as waist circumference, waist-to-hip ratio and hip circumference. From this, they identified 743 genetic regions linked to obesity, 86 of which hadn't been reported before.

Next, the researchers checked which tissues showed obesity-linked effects caused by the gene variations in those regions, such as on the production of insulin, a hormone that regulates blood sugar levels. They found that these genes fit into 11 clusters, each characterised by distinct biological pathways.



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We may be starting to work out why exercise doesn't help everyone lose weight

They are: metabolically unhealthy obesity; metabolically healthy obesity; six types that relate to the production of insulin; and types connected to immune system dysregulation, hormonal control of appetite and body weight, and lipid metabolism

One proposed form of obesity relates to metabolism of lipids



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(medRxiv, doi.org/pwvp).

The team calls these clusters endotypes, not subtypes, because the latter are typically mutually exclusive and people could only have one. Instead, an endotype reflects a distinct underlying biological mechanism, but several could coexist within an individual with varying degrees of influence.

The researchers validated their endotypes using separate data on more than 48,000 people in the Mass General Brigham Biobank.

"It is clear that there are many forms of obesity," says Frank Greenway at Louisiana State University in Baton Rouge. We already know that some people with obesity don't lose weight when taking GLP-1 drugs like Ozempic or Wegovy, which suggests that sometimes these aren't addressing the physiological problem, he says.

Gaining a better understanding of obesity and the forms it can take may eventually improve how we approach it. "In acknowledging that there are many different types of obesity, it may be possible to better target treatments and preventative interventions to provide more personalised care," says Laura Gray at the University of Sheffield, UK.

As six of the 11 endotypes are related to insulin, some interventions could be effective across several of the clusters, says team member Min Seo Kim, also at the Broad Institute.

The findings may change our interpretation of studies that looked at how genes and lifestyle interact in obesity, which has generally been treated as one condition, and may alter how such research is done going forward, says Kim.

Gray says there could even be more than 11 endotypes. That number was limited by the genetic regions that we know relate to obesity and the size of the genome datasets used to investigate the condition, she says.

"It's not just about the body mass index; it's more about the biology behind it"

Kim also believes the story might not be quite over yet. "I think it's possible that additional endotypes may be uncovered in the future, as genetic discovery continues," he says.

But Henriette Kirchner at the University of Lübeck in Germany says there could turn out to be fewer than 11 endotypes. She expects we will gain a greater understanding as other researchers try to replicate these findings. "I like the ideas of obesity clusters, but they have to be more refined in the future to be helpful in the clinics." ▮

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