# Overweight causes heart failure: Large study with new method clarifies the association

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An international research team led by Swedish scientists has used a new method to investigate obesity and overweight as a cause of cardiovascular disease. Strong association have been found previously, but it has not been clear whether it was overweight as such that was the cause, or if the overweight was just a marker of another underlying cause, as clinical trials with long-term follow-ups are difficult to implement.

A total of nearly 200,000 subjects were included in the researchers' study of the causality between obesity/overweight and diseases related to cardiovascular conditions and metabolism, which is being published for the first time in *PLOS Medicine*. The goal was to determine whether obesity as such is the actual cause of these diseases or whether obesity is simply a marker of something else in the subject's lifestyle that causes the disease.

"We knew already that obesity and cardiovascular disease often occur together. However, it has been hard to determine whether increased BMI as such is dangerous. In this study we found that individuals with gene variants that lead to increased body-mass index (BMI) also had an increased risk of heart failure and diabetes. The risk of developing diabetes was greater than was previously thought," says Tove Fall, a researcher at the Department of Medical Sciences and the Science for Life Laboratory, Uppsala University, who coordinated the study together with researchers from the Karolinska Institutet and Oxford University.

These scientists studied whether a gene variant in the FTO gene, which regulates the appetite and thereby increases the individual's BMI, is also linked to a series of cardiovascular diseases and metabolism. The risk variant is common in the population, and each copy of the risk variant increases BMI by an average of 0.3-0.4 units. Since an individual's genome is not affected by lifestyle and social factors, but rather is established at conception, when the embryo randomly receives half of each parent's genome, the method is thus called "Mendelian randomization". To achieve reliable results a large study material was needed, and nearly 200,000 individuals from Europe and Australia participated.

"Epidemiological studies look for associations in large populations, but it is usually difficult to reliably determine cause and effect – what we call causality. By using this new genetic method, Mendelian randomization, in our research, we can now confirm what many people have long believed, that increased BMI contributes to the development of heart failure. We also found that overweight causes increases in liver enzymes . This knowledge is important, as it strengthens the evidence that forceful societal measures need to be taken to counteract the epidemic of obesity and its consequences," says Erik Ingelsson, professor at the Department of Medical Sciences and the Science for Life Laboratory, Uppsala University.

The results show that an increase of one unit of BMI increases the risk of developing heart failure by an average of 20 per cent. Further, the study also confirms that obesity leads to higher insulin values, higher blood pressure, worse cholesterol values, increased inflammation markers, and increased risk of diabetes.

The present study was carried out within the framework of the major research consortium ENGAGE, which brings together more than 35 studies and more than 130 co-authors. The study was coordinated by

Erik Ingelsson's research group in collaboration with the Karolinska Institutet and Oxford University.

**More information:** "The Role of Adiposity in Cardiometabolic Traits: A Mendelian Randomization Analysis". Tove Fall, Sara Hägg, Reedik Mägi, [more than 125 additional authors], Nancy L. Pedersen, Mark I. McCarthy, Erik Ingelsson, Inga Prokopenko for the European Network for Genetic and Genomic Epidemiology (ENGAGE) consortium. *PLOS Medicine*. In press.

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