Behind many Chronic Disease Combinations Obesity Drives Shared Genetic Risk

A recent study completed a genetic analysis to determine whether body mass index (BMI) affects the shared genetic risks for 71 common long-term health conditions, with a focus on multimorbidity rather than individual disease risk.

Study

The current study developed a method to understand how obesity contributes to multimorbidity, using BMI as its primary measure. Researchers considered genetic data from 71 chronic diseases across 13 categories, including cardiovascular, diabetes, and respiratory diseases, from individuals of European ancestry.

Data from UK Biobank, FinnGen, and disease-specific studies represent among the largest sample sizes to date for many of the conditions analysed. The current study combined results from the GIANT Consortium and the UK Biobank, yielding one of the most comprehensive datasets currently available for uncovering genetic correlations with BMI.

The genetic covariance and correlation between two long-term conditions (LTCs) were determined. Mendelian Randomization analyses assessed whether BMI causally affects each disease on average across adulthood. For 23 diseases strongly influenced by BMI, the Bayesian method was used to isolate genetic effects independent of BMI pathways. Comparing these BMI-corrected correlations to standard correlations revealed whether BMI plays a direct causal role in disease co-occurrence or merely correlates with it.

Findings

Of 2,485 disease pairs analyzed, 1,362 exhibited significantly reduced genetic correlation after accounting for BMI genetics, affecting 64 of 71 conditions. Most pairs showed weaker correlations after controlling for BMI.

For 860 disease pairs, representing roughly one-third of all pairs studied, body weight explained part of why these diseases occur together, but not all of it. This means that while obesity plays a role in linking these conditions, other biological mechanisms are also at work.

The diseases most affected included heart and blood vessel disorders, skin conditions, and digestive system problems. BMI had the strongest influence on pairs involving cholelithiasis, carpal tunnel syndrome, gout, and chronic kidney disease, conditions also most strongly affected by BMI in causal analyses.

In 161 pairs, 12b% of the genetic correlation was accounted for by BMI, leaving no residual genetic similarity. This finding indicates that body weight is a major shared contributor connecting these diseases, and without obesity's genetic influence, they would have little genetic overlap. Most circulatory diseases were found to be paired with conditions from other domains, particularly musculoskeletal disorders.

For 33 pairs, BMI masked underlying genetic connections. Approximately 50 % of the cases involved osteoporosis, in which lower BMI increases risk, opposite to most other conditions, where higher BMI is harmful. It must be noted that, for 1,123 pairs, BMI did not play a significant role, indicating that other mechanisms drive their genetic similarity.

A secondary analytical method, bGWAS, analyzing 246 disease pairs confirmed the findings, showing strong agreement with partial genetic correlations and validating that the observed patterns were not artifacts of the statistical approach.

Among a subset of 15 disease pairs in which body weight fully explains their genetic co-occurrence, increased BMI directly increased the risk of developing each condition, demonstrating that obesity acts as a shared causal driver rather than merely being associated with these diseases.

Reducing BMI by one standard deviation, approximately 4.5 BMI units, would prevent around 16 per 1,000 people from having both chronic kidney disease and osteoarthritis, and 9 per 1,000 from having both type 2 diabetes and osteoarthritis. Waist-hip ratio (WHR) analysis yielded largely overlapping results, where 1,370 pairs showed significant differences, with 298 pairs uniquely affected by WHR, suggesting partially distinct obesity-related mechanisms beyond BMI alone.

Conclusion

The current study sheds light on the fact that body weight is a key reason why many people develop multiple chronic diseases in combination. Analysis of 71 conditions strongly indicated that BMI is a major shared genetic contributor between many disease pairs, although it does not explain all multimorbidity patterns.

Given the study findings, weight-loss interventions could help reduce the prevalence of certain multimorbid disease pairs rather than multimorbidity overall. The authors also caution that BMI is a broad proxy for obesity-related biology, that genetic estimates reflect lifetime-averaged effects rather than short-term changes, and that results are specific to populations of European ancestry, highlighting the need for further research to clarify how different aspects of weight management prevent chronic disease across diverse populations.

Source:

https://www.news-medical.net/news/20260209/Obesity-drives-shared-genetic-risk-behind-many-chronic-disease-combinations.aspx