Clinically useful obesity subtypes revealed by harnessing deviations from population-average risk

Obesity is associated with many life-threatening comorbidities. Its heterogeneous risk profile makes the prevention of obesity and its pathogenic consequences challenging. In this study, the heterogeneous relationships between body mass index and ten cardiovascular risk markers were quantified using machine learning, from which powerful clinical prediction models were developed and validated.

This is a summary of:
Coral, D. E. et al. Subclassification of obesity for precision prediction of cardiometabolic diseases. *Nat. Med.* https://doi.org/10.1038/s41591-024-03299-7 (2024).

Published online: 17 January 2025

The question

Obesity is a common, highly heterogeneous and multimorbid condition that often coexists with a range of cardiometabolic abnormalities[1]. The simplicity with which obesity is defined (using body mass index (BMI) thresholds) belies its complexity and the major barriers to its prevention and treatment. Accurately predicting long-term clinical outcomes attributable to obesity is also difficult, with some people with obesity appearing healthy, and others experiencing severe health consequences[2]. Improving the diagnostic subclassification of obesity is a logical step towards addressing these challenges. The use of machine learning to combine complex data and define hidden structures in health datasets is an increasingly popular method[3,4]. Heterogeneous disorders like obesity are obvious targets for such approaches.

The observation

To investigate the heterogeneity between obesity and cardiometabolic risk, the study utilized unsupervised machine learning techniques applied to datasets comprising over 173,000 participants from four European cohorts. We analyzed the relationships between BMI and ten standard clinical biomarkers of cardiovascular and metabolic health. These biomarkers included markers of lipids, glycemia, inflammation, hepatic function and blood pressure. Deviations from expected BMI–biomarker relationships were visualized using nonlinear dimensionality reduction methods, which informed the clustering of individuals into phenotypic profiles, enabling the identification of groups with atypical cardiometabolic risk patterns (Fig. 1a). This approach was validated in independent cohorts to ensure robustness and transferability.

We found that individuals with certain discordant patterns had increased cardiovascular risk. For instance, those with a discordant lipid profile relative to their BMI showed a significantly increased incidence of coronary artery disease and stroke (Fig. 1b). Current risk assessment models fail to account for this excess risk. The improvements in prediction obtained by incorporating discordant profiles into these models is comparable to the improvements gained from established risk factors such as low-density lipoprotein (LDL) cholesterol. The benefits of our approach were most pronounced in individuals with predominantly concordant profiles, emphasizing the value of using probabilistic profiling to uncover subtle risk variations.

Future directions

The paper describes a novel approach that combines existing clinical data to define risk profiles that are consistent with population-average risk expectations, and those that diverge from those expectations. In this example, the method was applied to the subclassification of obesity and the precision prediction of cardiovascular disease. Although this example illustrates how the approach can improve the predictive accuracy of a widely deployed risk prediction algorithm (SCORE2), there are many potential applications — for example, for diverse disease outcomes or using other input data.

The research focuses on maximizing prediction accuracy using standard clinical biomarkers of cardiovascular risk. The method does not seek to define risk profiles that are necessarily causally related to cardiovascular disease. Thus, it remains to be determined whether the risk profiles described in this paper represent effective treatment targets. A second important caveat relates to the transferability of the findings to diverse populations. The primary analyses in this paper were undertaken in European ancestry cohorts living in northern Europe, with validation performed in people of African and South Asian ancestry from the UK. It is unknown whether the profiles would replicate in other ancestry groups in the UK or in populations of any ancestry living outside northern Europe.

Our next steps include applying this subclassification approach to diverse clinical outcomes and using other types of input data beyond standard clinical markers. We will also examine whether the subclassification profiles influence outcomes in interventional settings, to assess the extent to which targeting treatment to profile improves clinical outcomes.

Daniel E. Coral & Paul W. Franks
Department of Clinical Sciences, Lund University, Helsingborg, Sweden.

EXPERT OPINION

"The paper addresses a very important question in clinical medicine, namely determination of the cardiovascular risk of a given BMI at the individual level. Although BMI is regularly used to assess clinical risk at the individual level, it differs from actual risk in a considerable number of patients and partially misinterprets body composition. The findings can be considered a step forward in cardiometabolic individualized medicine and might help to guide treatment decisions." **Andreas L. Birkenfeld, Universitätsklinikum Tübingen, Tübingen, Germany.**

FIGURE

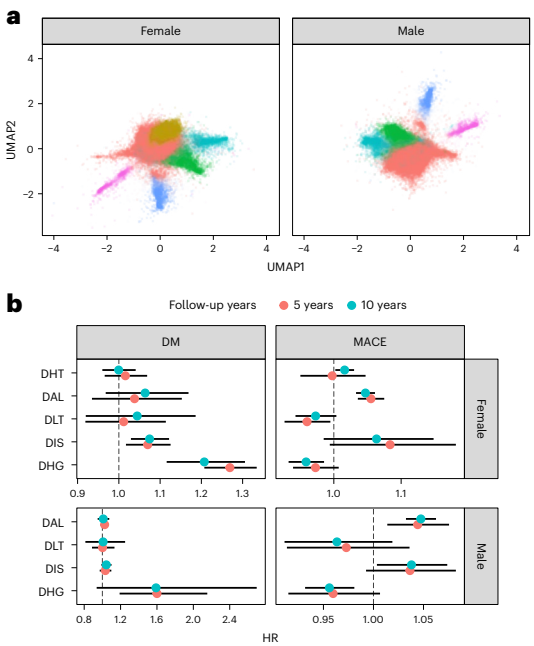

Fig. 1 | Concordant and discordant BMI-biomarker profiles. a, Nonlinear dimension reduction of discordance using the uniform manifold approximation and projection (UMAP) method. We found one concordant profile and four discordant profiles in men and five in women. Colors denote profile allocations. **b**, Hazard ratios (HRs) and 95% confidence intervals associated with a 10% probability shift from the concordant profile to each of the discordant profiles. DAL, discordant adverse lipid profile; DHG, discordant hyperglycemic profile; DHT, discordant hypertensive profile; DIS, discordant inflammatory state profile; DLT, discordant liver transaminases profile; DM, diabetes mellitus; MACE, major adverse cardiovascular event.

BEHIND THE PAPER

Precision medicine solutions rely on successfully separating two key sources of data heterogeneity: first, the 'signal' (markers of biological features that drive causal processes); and second, the 'noise' (the systematic and non-systematic errors that exist in all datasets)[4]. We developed the 'discordancy' approach to address this challenge, focusing on identifying individuals whose clinical features diverge from population-average expectations. The approach was developed through a series of papers in which we juxtaposed disease features, with each iteration moving closer to a clinically useful result. In one 2023 paper[5], for example, we used polygenic risk scores to contrast obesity and type 2 diabetes risk. Using this approach, we showed that individuals who were genetically discordant for these traits (higher obesity risk and lower diabetes risk) were characterized by a healthier cardiometabolic risk profile than those who were genetically concordant. However, the discordant group had a higher predisposition to other health risks, including osteoarthrosis and ulcerative colitis. **D.E.C. & P.W.F.**

REFERENCES

1. Zhou, X. D. et al. Burden of disease attributable to high body mass index: an analysis of data from the Global Burden of Disease Study 2021. *eClinicalMedicine* **76**, 102848 (2024).
   Study analyzing the global effects of obesity on health.
2. Prillaman, M. Why BMI is flawed — and how to redefine obesity. *Nature* **622**, 232–233 (2023).
   This paper discusses the limitations of using BMI as the primary diagnostic tool for obesity.
3. Tobias, D. K. et al. Second international consensus report on gaps and opportunities for the clinical translation of precision diabetes medicine. *Nat. Med.* **29**, 2438–2457 (2023).
   A systematic review of the evidence of precision medicine approaches in diabetes.
4. Franks, P. W. & Sargent, J. L. Diabetes and obesity: leveraging heterogeneity for precision medicine. *Eur. Heart J.* **45**, 5146–5155 (2024).
   A state-of-the-art review on approaches to precision medicine in diabetes and obesity.
5. Coral, D. E. et al. A phenome-wide comparative analysis of genetic discordance between obesity and type 2 diabetes. *Nat. Metab.* **5**, 237–247 (2023).
   Genetic analysis of discordance between BMI and diabetes.

FROM THE EDITOR

"According to this study, the use of unsupervised clustering to identify unique phenotypic profiles with atypical BMI–risk biomarker relationships could help to avoid unnecessary interventions while supporting the initiation of appropriate interventions for large numbers of individuals at risk of cardiometabolic disease. Such precision medicine-based approaches, when implemented across diverse populations, could revolutionize early risk prediction and the prevention of non-communicable diseases." **Editorial Team, *Nature Medicine*.**