

Personalized Medicine for Obesity: A Genomics Perspective

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PRECISION
MEDICINE



Heterogeneity

- Why do some of us go on and develop diabetes, cancer, obesity... Etc?
- Why do some of us develop severe forms of these diseases yet others do not?
- Why do some of us respond positively to medications/interventions while others do not?





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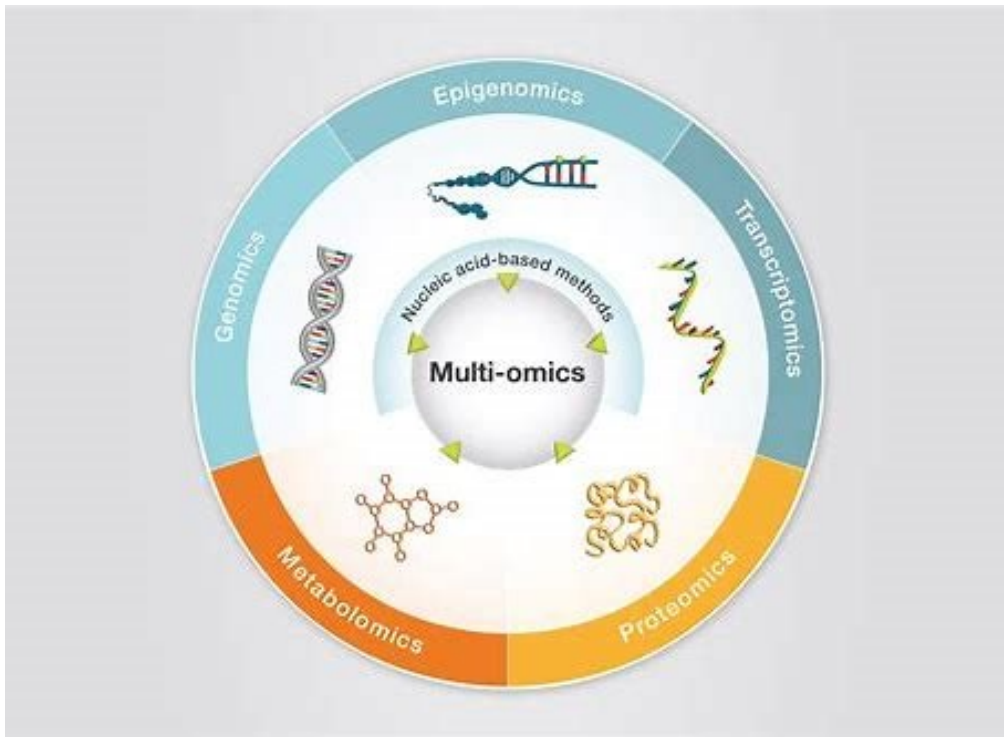
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The Human Genome Project

The blueprint that allowed us to answer
most of these questions...

The Human Genome Project and Omics Disciplines

A catalyst for...



- **Genomics** involves the comprehensive study of the entire genome, which includes sequencing, mapping, and analyzing DNA to understand genetic variations and functions.
- **Transcriptomics** focuses on the transcriptome, analyzing all RNA molecules to understand gene expression levels and regulation mechanisms in different conditions.
- **Proteomics** examines the entire set of proteins, looking at protein expression, structure, and functions to gain insights into cellular processes.
- **Metabolomics** analyzes the metabolome, which includes small molecules and metabolites, to understand metabolic pathways and physiological states.
- **Epigenomics** explores epigenetic changes, such as DNA methylation and histone modification, which influence gene expression without altering the genetic code.

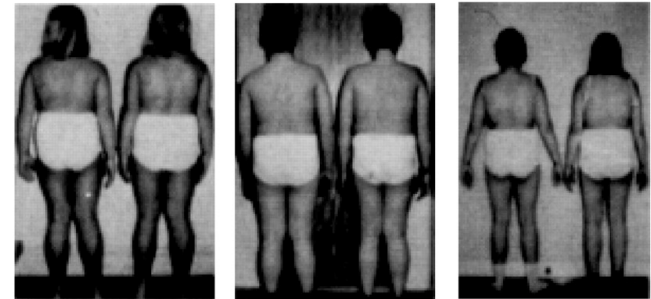
Historical Context

Genetic Insights on Obesity Before the Human Genome Project

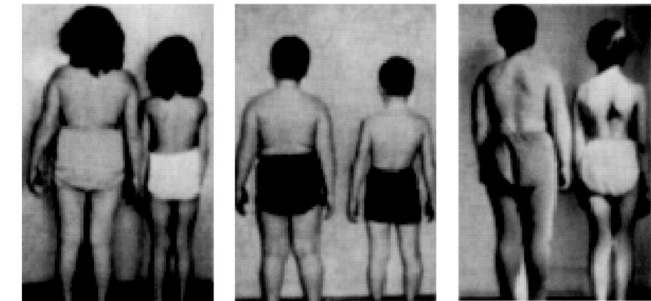
Two Key Genetic Discoveries Pre-HGP

- **Familial Studies:** Observational studies in families and twins established that obesity has a heritable component, with heritability estimates ranging from 40% to 70%.
- **Single-Gene Disorders (1997):** Rare cases of monogenic obesity (caused by mutations in a single gene).
 - LEP (Leptin gene): Mutations in this gene were linked to severe early-onset obesity
 - Undetectable serum leptin levels and resulting in disruption in appetite regulation.
 - Accounted for less than 1% of cases

Body Mass in Twins



Monozygotic Twins (Intrapair Correlation = 0.66)



Dizygotic Twins (Intrapair Correlation = 0.26)

Cost per Human Genome



Timeline of Key Genetic Findings Related to Obesity after The Human Genome Project



Major Milestones in identifying genomic variations associated with obesity

- **2007: First Genome-Wide Association Studies (GWAS).** The FTO gene was discovered as the first gene linked to fat mass and obesity, indicating variants that increase obesity and type 2 diabetes risk.
- **2010s: Continuation to study candidate-genes along with GWAS** Identified numerous genetic variants associated (e.g. MC4R gene variants) with BMI and obesity, showcasing the complexity of genetic factors.
- **2015: First Meta-GWAS** showcasing the complexity of genetic factors associated
- **2018: Polygenic Risk Scores (PRS)** that summarize the impact of multiple genetic variations on obesity risk.

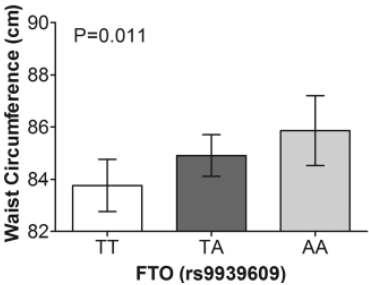
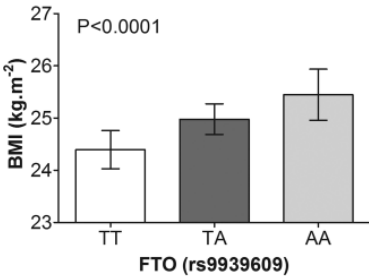
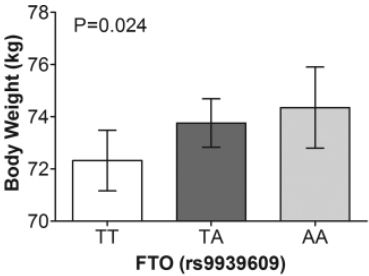
2007: First GWAS

A Common Variant in the *FTO* Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity


TIMOTHY M. FRAYLING, NICHOLAS J. TIMPSON, MICHAEL N. WEEDON, ELEFTHERIA ZEGGINI, RACHEL M. FREATHY, CECILIA M. LINDGREN, JOHN R. B. PERRY,

KATHERINE S. ELLIOTT, HANA LANGO, [...], AND MARK I. MCCARTHY [+32 authors](#) [Authors Info & Affiliations](#)

SCIENCE • 11 May 2007 • Vol 316, Issue 5826 • pp. 889-894 • DOI:10.1126/science.1141634



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HEALTH: WEBMD

Obesity in the Genes?

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April 12, 2007 / 4:00 PM EDT / WebMD

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Clear obesity gene link 'found'

Scientists say they have identified the clearest genetic link to obesity yet.

They found people with two copies of a "fat" version of a gene had a 70% higher risk of obesity than those with none, and weighed 3kg (6.5lb) more.

The work in Science by the Peninsula Medical School and Oxford University studied data from about 40,000 people.



Scientists have found a clear genetic link to obesity

2008-2015: More genomic variations associated with obesity were being discovered...

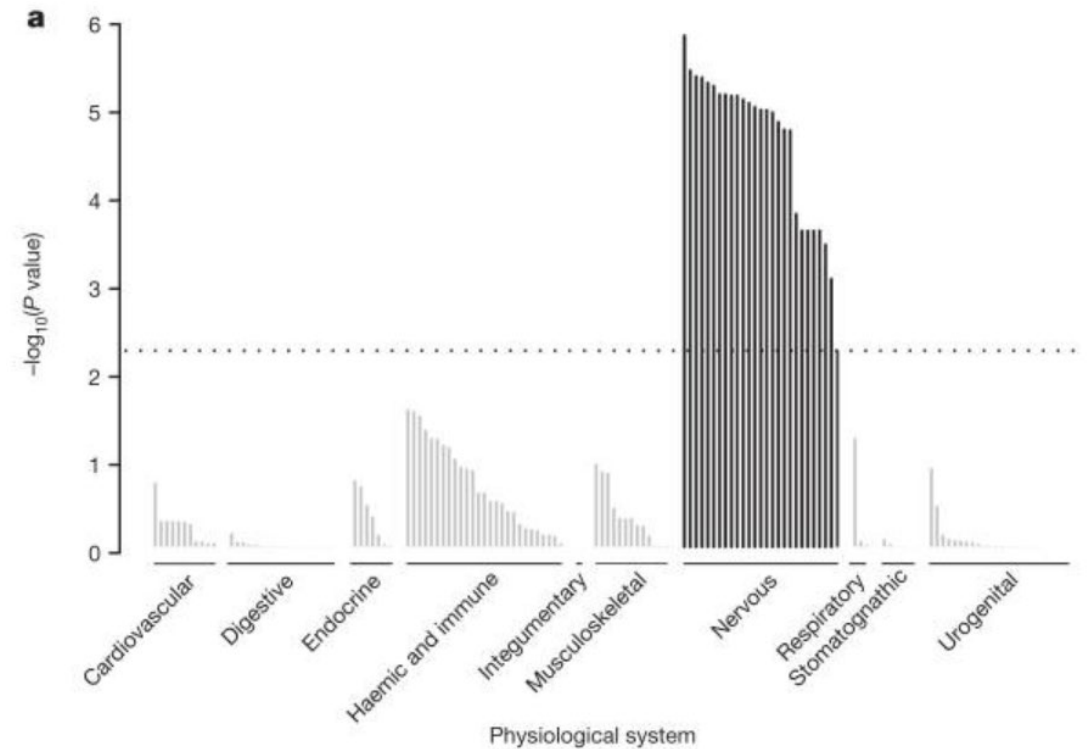
nature

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Article | Published: 11 February 2015

Genetic studies of body mass index yield new insights for obesity biology



A.M.A. Recognizes Obesity as a Disease

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Sugary diets and weight problems remain a central health issue. Mamta Popat/Arizona Daily Star, via Associated Press

[A.M.A. Recognizes Obesity as a Disease - The New York Times](#)

Kate Dailey

BBC News Magazine

25 June 2013

Last week, the American Medical Association voted to classify obesity as a disease. But is being fat the same thing as being sick?

The decision came at the annual meeting of the American Medical Association (AMA).

[Obesity is a disease in the US. Should it be? - BBC News](#)

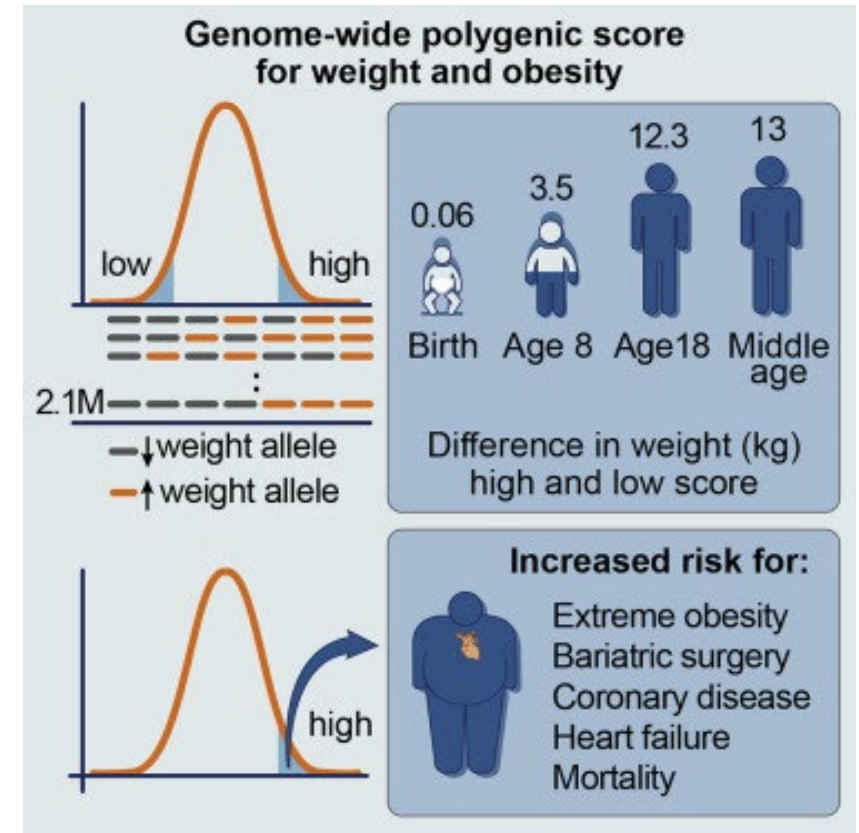
2019: Polygenic/genetic risk scores - can we predict who will develop obesity?

ARTICLE · Volume 177, Issue 3, P587-596.E9, April 18, 2019 · [Open Archive](#)

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Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood

[Amit V. Khera](#)^{1,2,3,4,15} · [Mark Chaffin](#)^{3,15} · [Kaitlin H. Wade](#)^{5,6,7} · ... · [Nicholas J. Timpson](#)^{5,6,7} · [Lee M. Kaplan](#)^{4,8} · [Sekar Kathiresan](#)^{1,2,3,4,16} · ... [Show more](#)



2022: Monogenic obesity – Is it now more common than what we thought?

International Journal of Obesity

www.nature.com/ijo

ARTICLE

Testing for rare genetic causes of obesity: findings and experiences from a pediatric weight management program

Karyn J. Roberts^{1,2}, Adolfo J. Ariza^{2,3,4}, Kavitha Selvaraj^{2,3}, Maheen Quadri^{2,3}, Caren Mangarelli^{2,3}, Sarah Neault³, Erica E. Davis^{2,4} and Helen J. Binns^{2,3,4}

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Check for updates

- More than 100 obese children were sequenced

- About 10% found to have a “**pathogenic**” or “**likely-pathogenic**” mutation

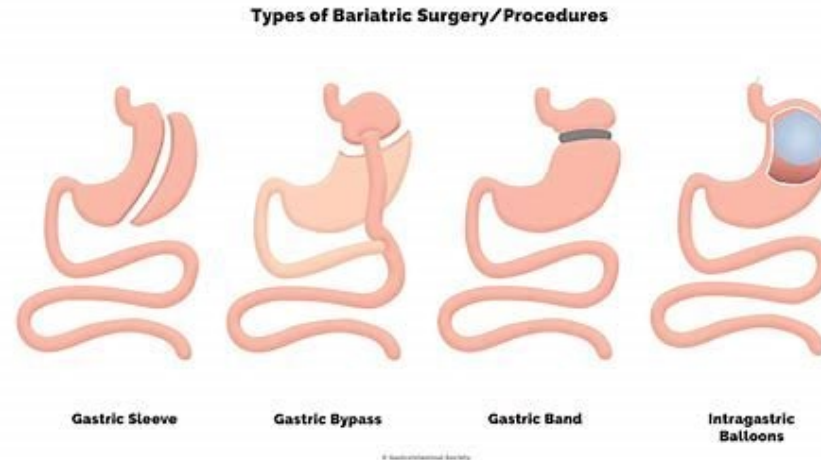
- 38.5% had a **variant of unknown significance (VUS)** within a gene that has been reported to be correlated with obesity



Can genomic variation influence weight loss after interventions?



Pharmacogenomics



Surgigenomics



Nutrigenomics

Weight loss after obesity interventions are influenced by genetic variations

Diabetes, Metabolic Syndrome and Obesity

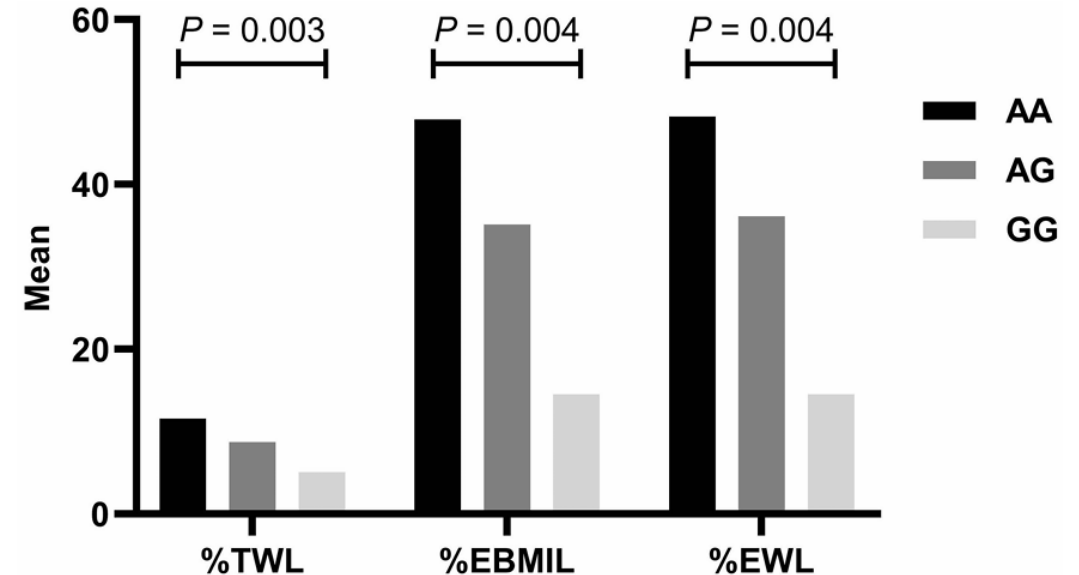
Dovepress

Open Access Full Text Article

ORIGINAL RESEARCH

Influence of the Brain-Derived Neurotrophic Factor Gene Polymorphism on Weight Loss Following Intra-gastric Balloon Intervention: A Cross-Sectional Study

Ahmad Al-Serri¹, Hessa A Al-Janahi¹, Mohammad H Jamal², Dana AlTarrah³, Ali H Ziyab⁴, Suzanne A Al-Bustan⁵



Polygenic/genetic risk scores have been used to predict/estimate weight loss outcomes

➤ [J Gastrointest Surg](#). 2024 Sep;28(9):1400-1405. doi: 10.1016/j.gassur.2024.05.029.
Epub 2024 May 29.

Use of polygenic risk scores to assess weight loss after bariatric surgery: a 5-year follow-up study

Elionora Peña ¹, Patricia Mas-Bermejo ², Albert Lecube ³, Andreea Ciudin ⁴, Concepción Arenas ⁵, Rafael Simó ⁴, Mercedes Rigla ⁶, Assumpta Caixàs ⁶, Araceli Rosa ⁷

- Similar studies have shown an AUC of 0.888
- Useful tool to predict surgical outcomes in advance
- Provides clinicians with a personalised management plan

Can we choose the best type of surgery?

Obesity Surgery
<https://doi.org/10.1007/s11695-019-04184-w>

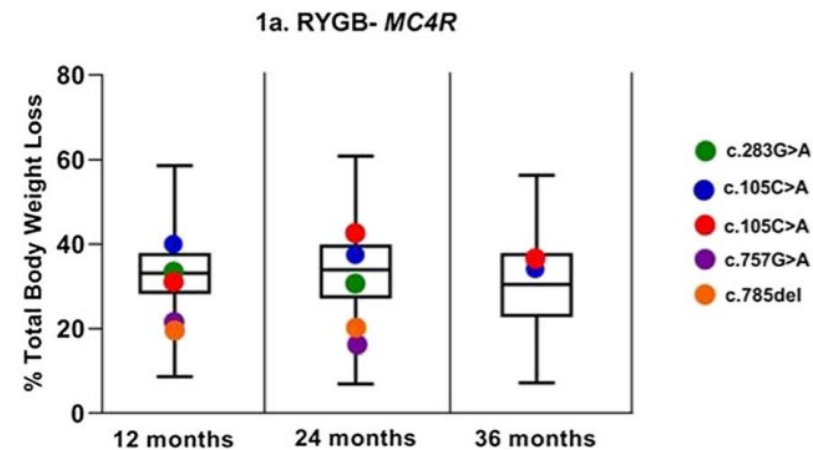
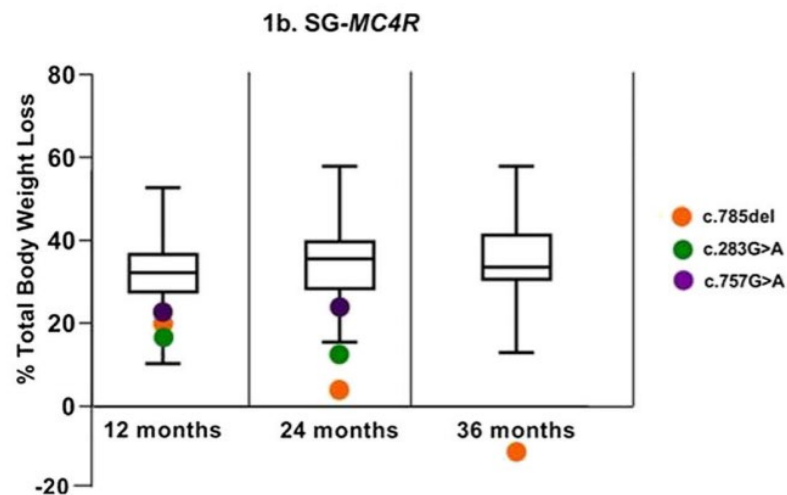


ORIGINAL CONTRIBUTIONS

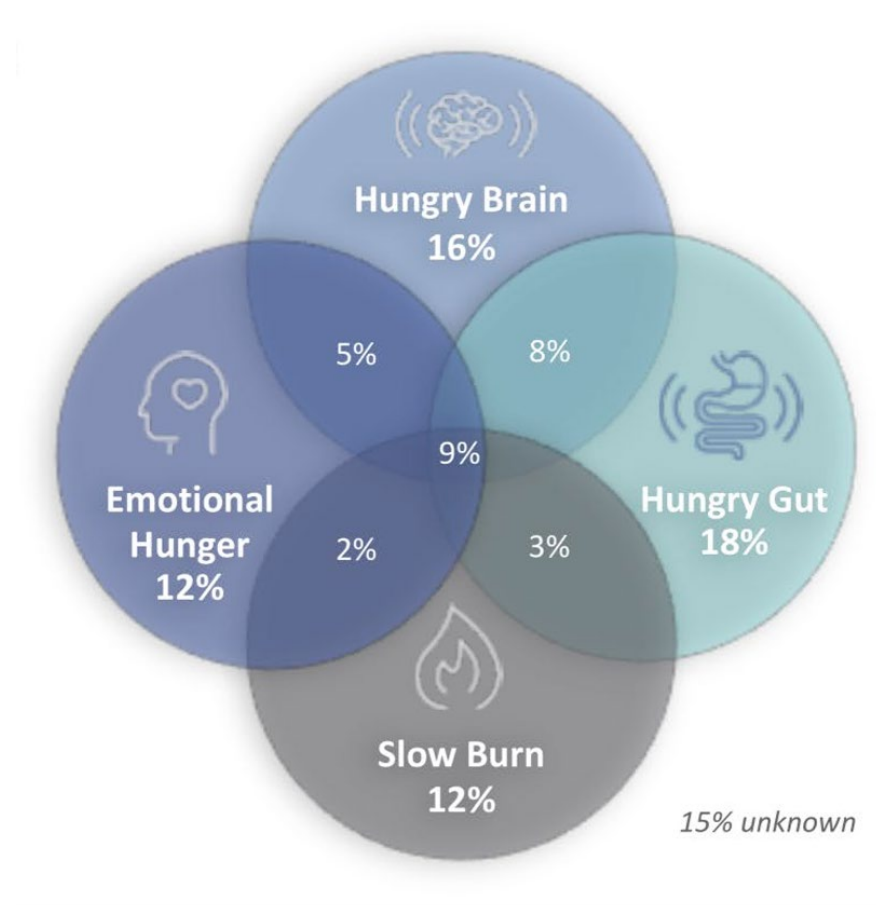


Genetic Obesity and Bariatric Surgery Outcome in 1014 Patients with Morbid Obesity

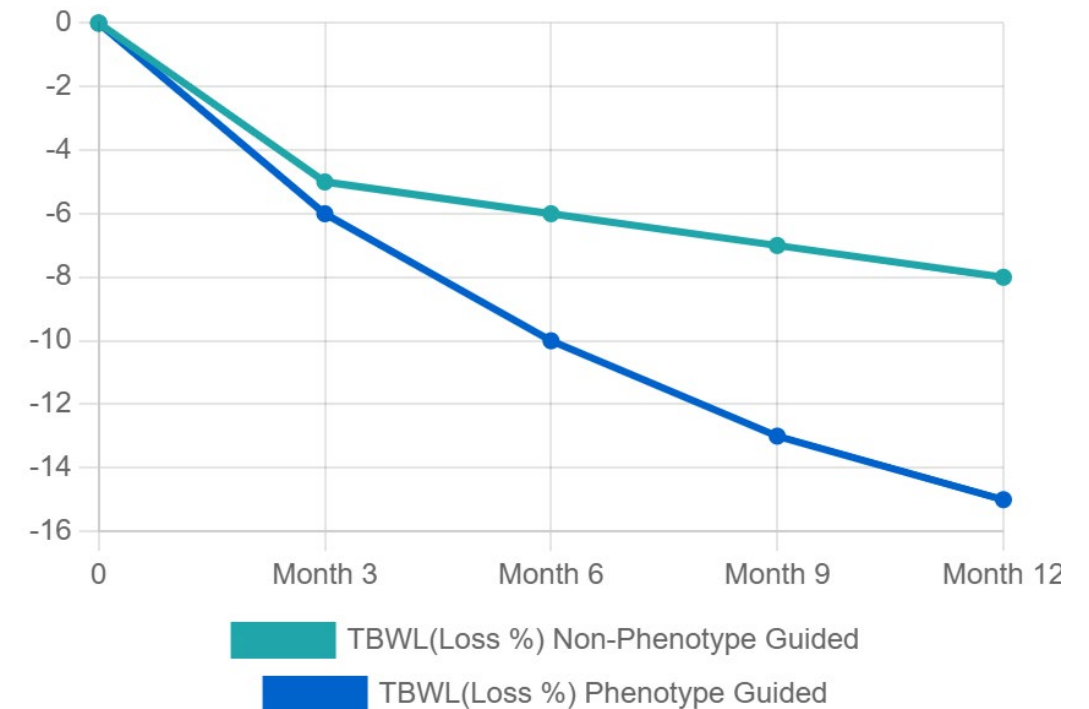
M.I. Cooiman^{1,2} · L. Kleinendorst³ · E.O. Aarts¹ · I.M.C. Janssen^{1,4} · H.K. Ploos van Amstel⁵ · A.I. Blakemore^{6,7} · E.J. Hazebroek¹ · H.J. Meijers-Heijboer^{2,3} · B. van der Zwaag⁵ · F.J. Berends¹ · M.M. van Haelst^{2,3}



Emerging research on redefining obesity phenotypes into subcategories...



Total Body Weight Loss (%)



Challenges to overcome and gaps to fill

Anticipating advancement in technology



Biobanks and longitudinal follow-ups



Are we ready?

TBM

SYSTEMATIC REVIEW

A scoping review of social and behavioral science research to translate genomic discoveries into population health impact

Caitlin G. Allen,¹ Shenita Peterson,² Muin J. Khoury,³ Lawrence C. Brody,⁴ Colleen M. McBride¹