



CENTER FOR  
COMPLEXITY  
& BIOSYSTEMS  
University of Milan

# Pathway deregulation in obesity

24 July 2015

—Como  
ISINP

Caterina A. M. La Porta  
Stefano Zapperi  
*University of Milan*



F. Font-Clos, S. Zapperi, C.A.M. La Porta  
NPJ Systems Biology & Applications 18, 2017  
doi:10.1038/s41540-017-0018-z

F. Font-Clos, S. Zapperi, C.A.M. La Porta  
BioRxiv doi: <https://doi.org/10.1101/159186>

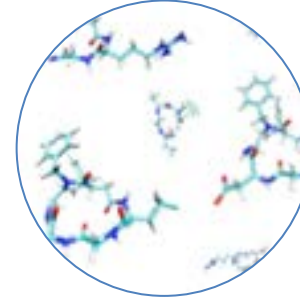
[WWW.COMPLEXITY.UNIMI.IT](http://WWW.COMPLEXITY.UNIMI.IT)

# RESEARCH

Neurodegenerative diseases



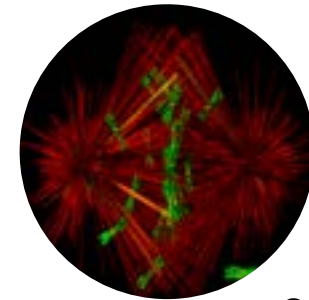
Protein/RNA simulations



Complex Networks & Data science



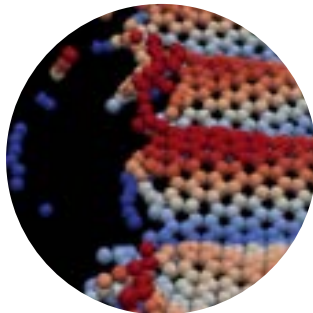
Cell division



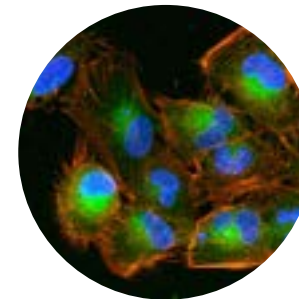
**C&B**  
CENTER FOR  
COMPLEXITY  
& BIOSYSTEMS  
University of Milan



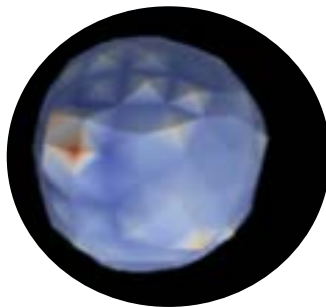
Disordered materials



Cancer



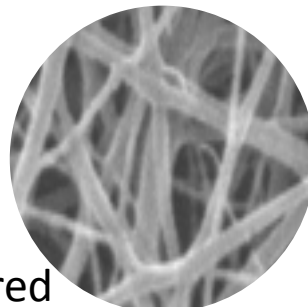
Cell biomechanics



Chromatin



Bio-inspired Materials (animals/plants)



# OBESITY: WHY DO WE CARE?

# OBESITY IS NOW A GLOBAL EPIDEMIC!



© iStock.com / Ernesto Victor Saúl Herrera Hernández

**THE WORLD IS GETTING FATTER**

250<sup>+</sup> MILLION PEOPLE 1980 → 904<sup>+</sup> MILLION PEOPLE 2008  
\*number of people who are either overweight or obese

**HOW DO I KNOW WHETHER I AM OVERWEIGHT?**

Calculate your body mass index (BMI) using this formula:  $BMI = \frac{\text{weight (kg)}}{\text{height}^2 (\text{m}^2)}$

Underweight < 18.5 | Normal 18.5 - 24.9 | Overweight 25 - 29.9 | Obesity > 30 | Severe Obesity > 35

**OBESITY IS KILLING PREVENTABLE THE WORLD**

**OBESITY KILLS!**  
 7 common diseases due to obesity:  
 • Arthritis • Cancer • Infertility • Heart Diseases  
 • Back Pain • Diabetes • Stroke

**ABC TO OBESITY PREVENTION**

**SIMPLE RULES TO STAY IN SHAPE**

**A** dopt New Healthy Habits

GOOD HABIT	Bike to Work	VS	Drive to Work	BAD HABIT
	Balanced Diet		Fast Food	
	Swim		Watch TV	

**B**alance Your Calorie Intake

Food Intake (CALORIES IN) vs Physical Activity (CALORIES OUT)

**C**ontrol Your Weight Gain

50

source: World Health Organization ©2014 Healthline www.healthline.com

# STATISTICS

## Adult Obesity Rate by State, 2014

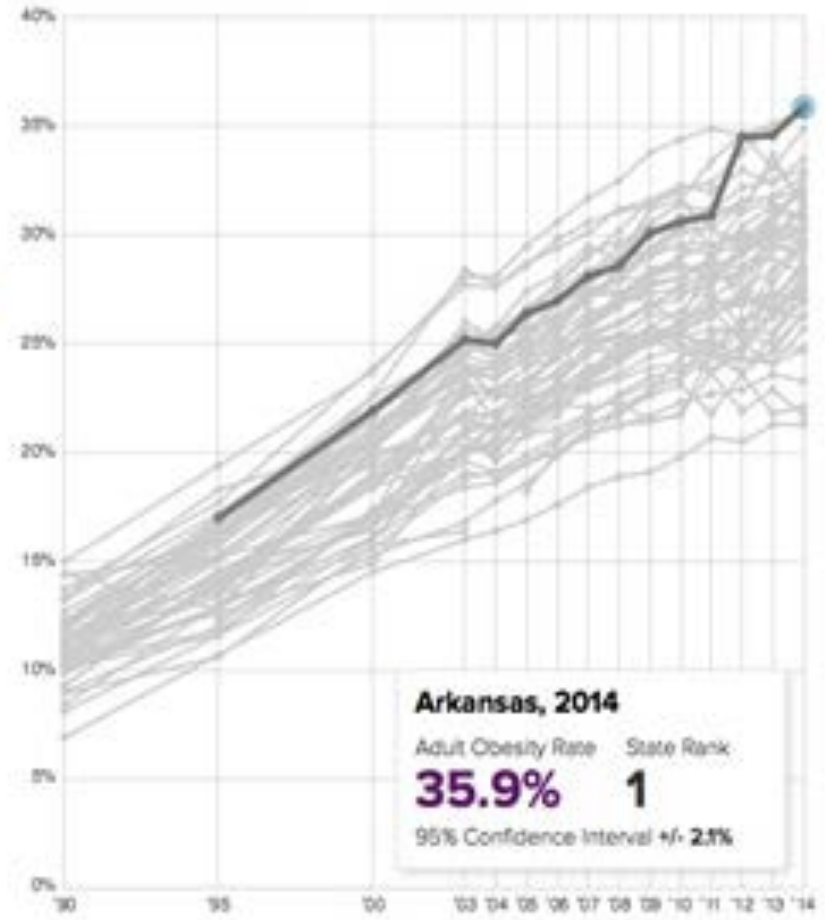
Select years with the slider to see historical data. Hover over states for more information. Click a state to lock the selection. Click again to unlock.

Percent of obese adults (Body Mass Index of 30+)

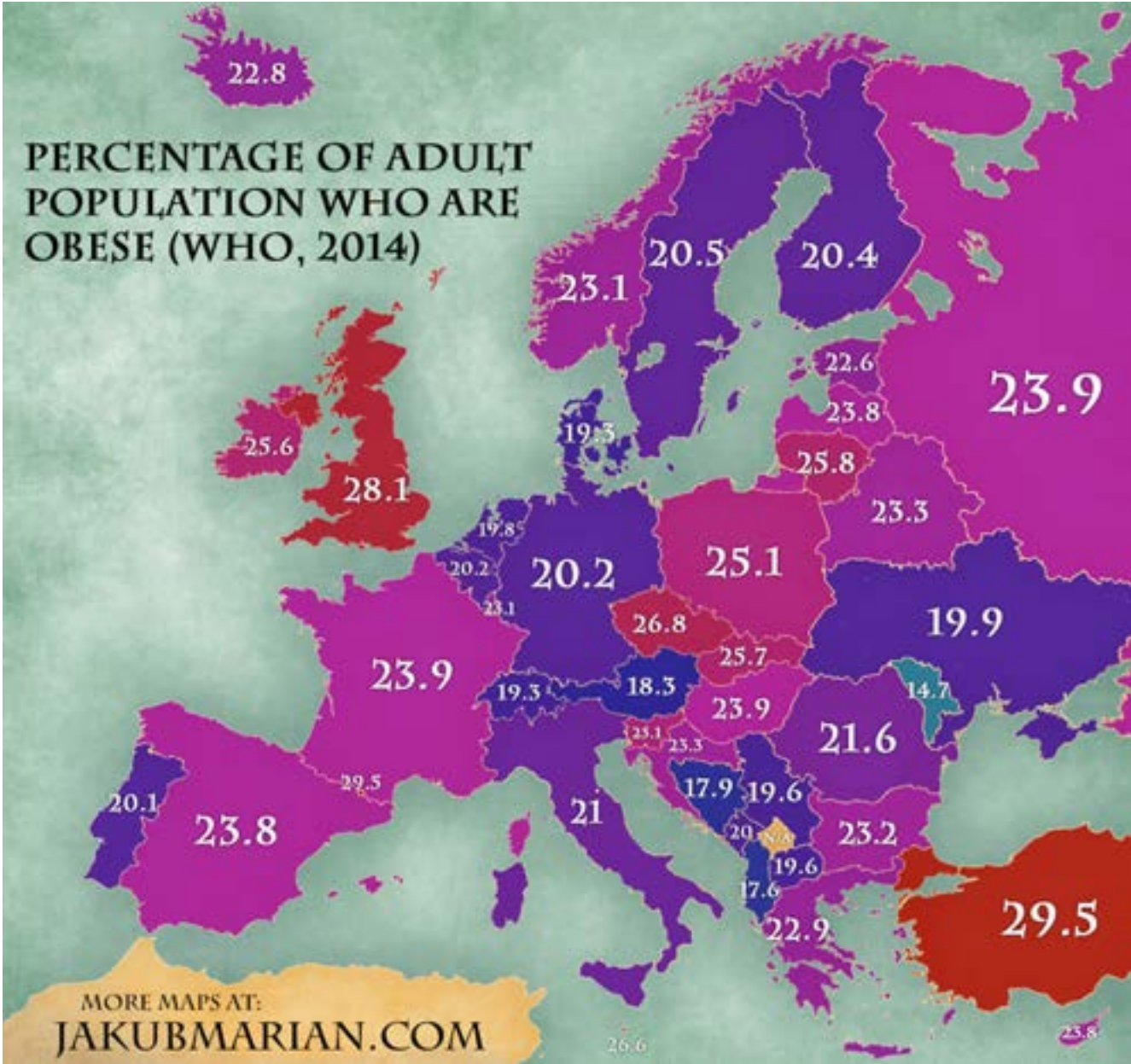
0 - 9.9% 10 - 14.9% 15 - 19.9% 20 - 24.9% 25 - 29.9% 30 - 34.9% 35%+



## Adult obesity rates, 1990 to 2014



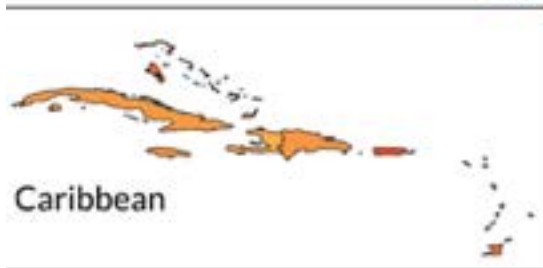
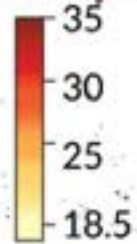
# STATISTICS



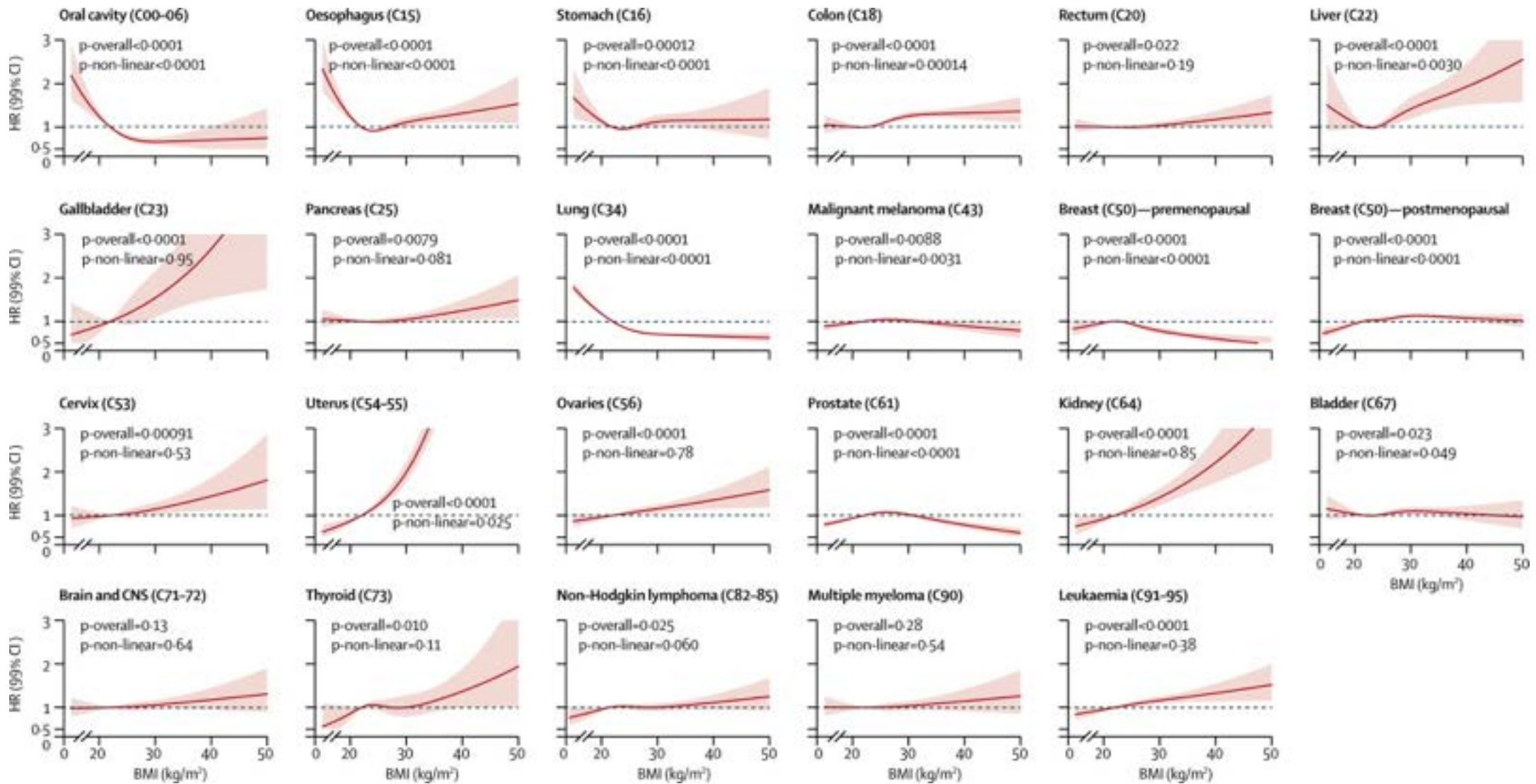
# STATISTICS

2014  
Men

Average  
BMI  
(kg/m<sup>2</sup>)

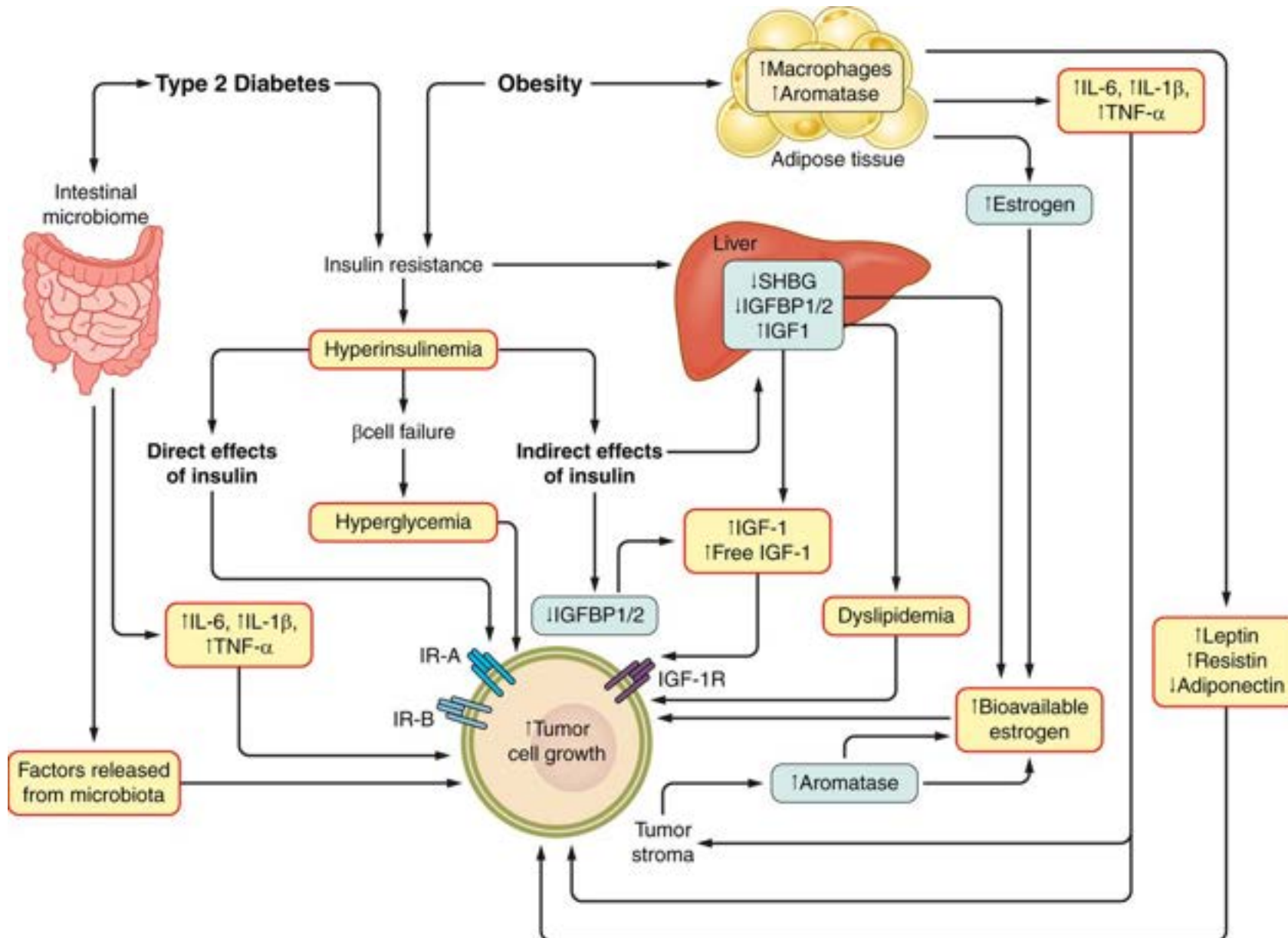


# CORRELATIONS BETWEEN CANCER AND OBESITY

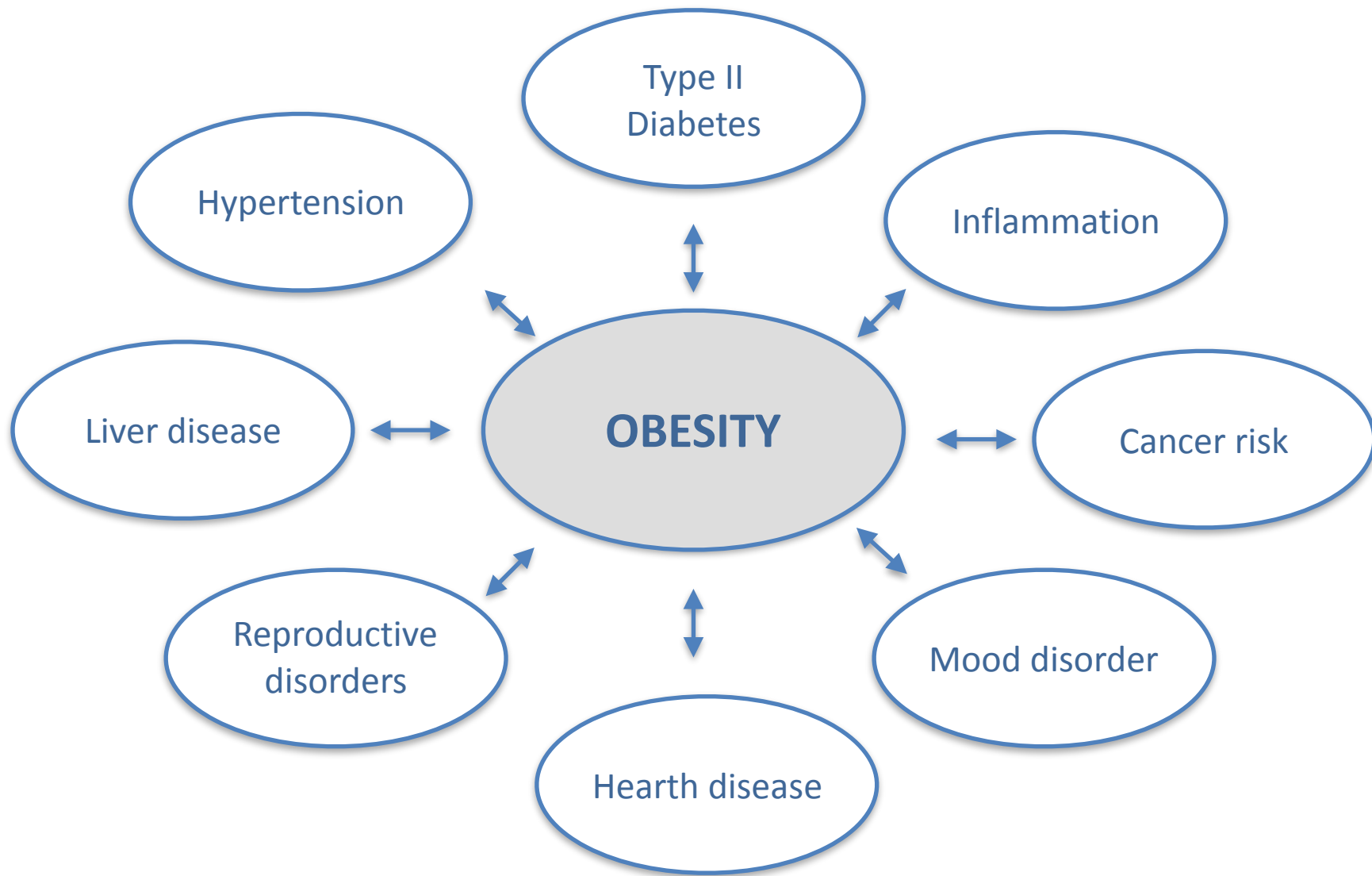


Body-mass index and risk of 22 specific cancers:  
 a population-based cohort study of 5.24 million UK adults  
 Bhaskaran, Krishnan et al. The Lancet, Volume 384, Issue 9945, 755 - 765

# BIOCHEMICAL NETWORKS







## GOAL

Transcriptomic data provides a picture of the alterations in regulatory and metabolic activities associated with obesity, but its interpretation is typically blurred by noise.

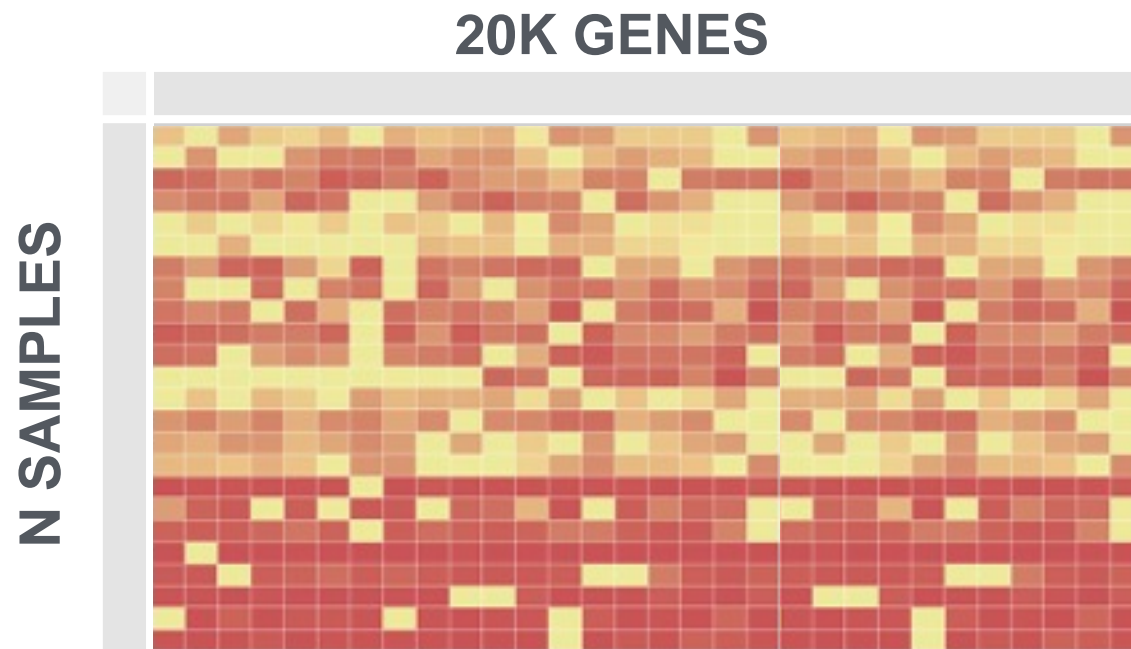
# STRATEGY

collecting publicly available transcriptomic data from adipocytes and blood with obese and type 2 diabetes and lean subjects

collecting publicly available transcriptomic data from adipocytes of breast cancer patients with known BMI and cancer history

collecting publicly available transcriptomic data from adipocytes of twins subjects

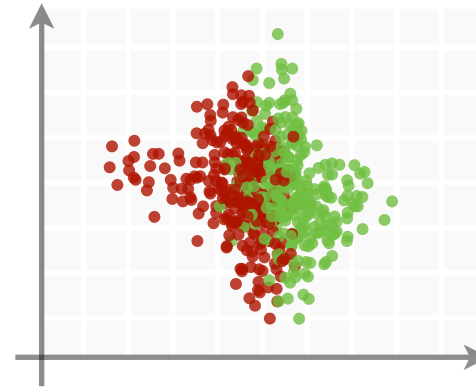
# TRANSCRIPTOMICS: THE CURSE OF DIMENSIONALITY



**#variables** is much larger than **#samples**

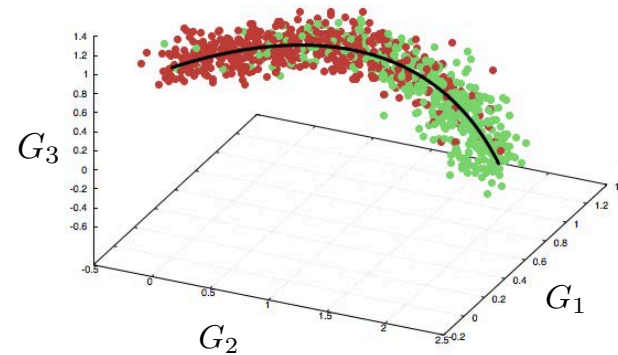
# SOLUTIONS

increase **#samples**



Spectral method to **merge datasets** and remove batch effects

decrease **#variables**



Nonlinear fitting to compute **pathway deregulation** scores

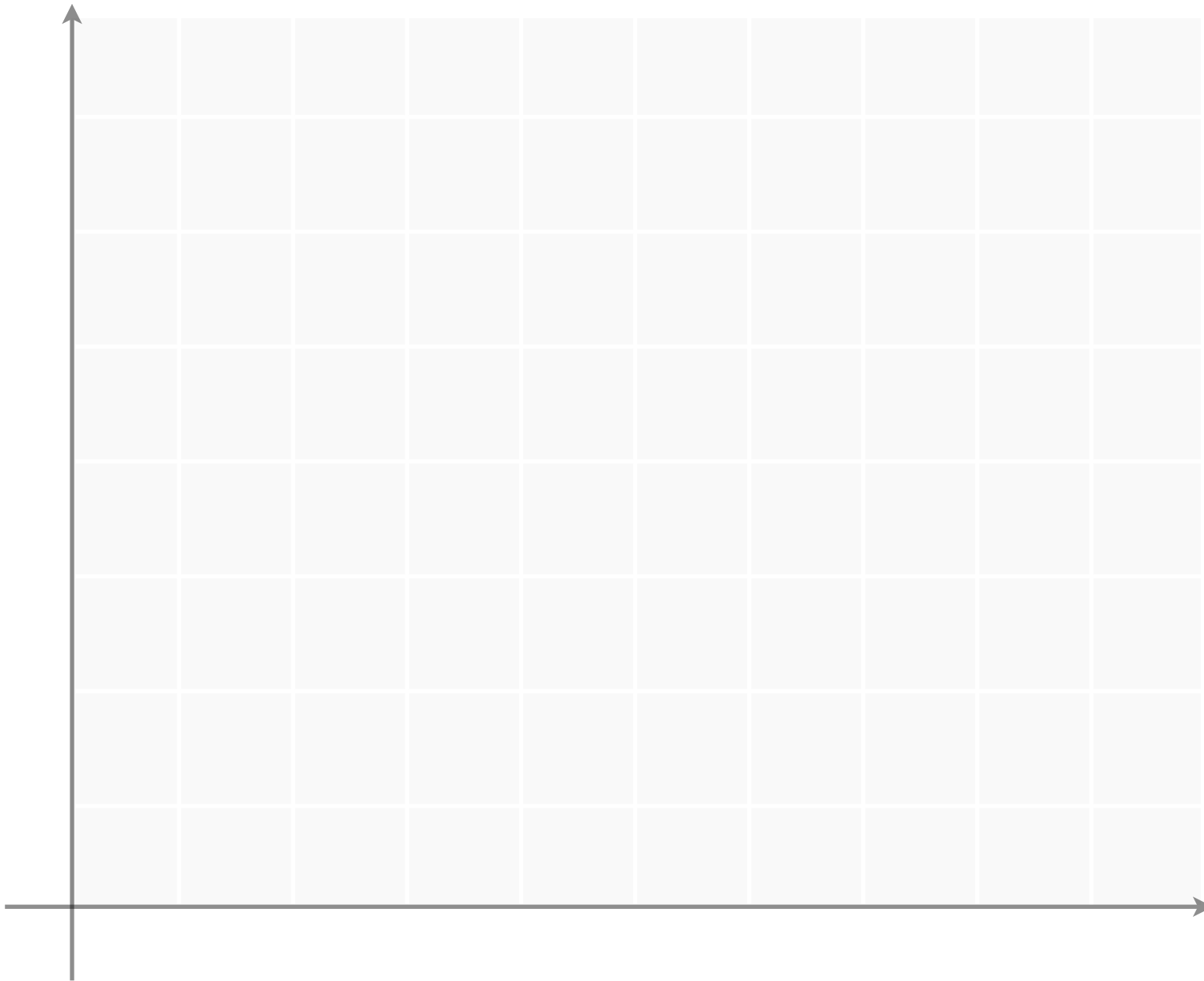


**44.35 TB** of archived data  
~**2.1M** assays  
~**68K** experiments

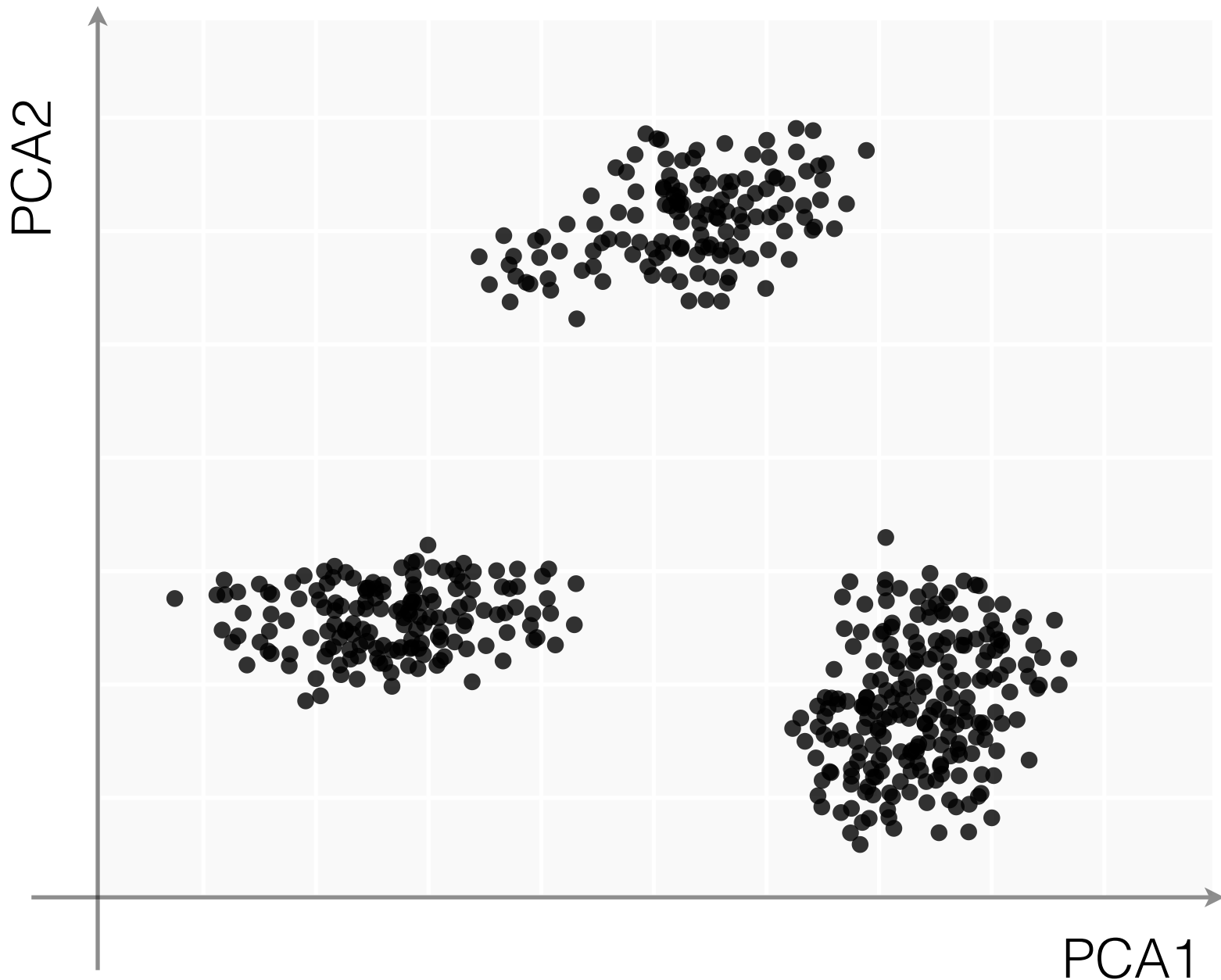
query = "obesity"

Download data!

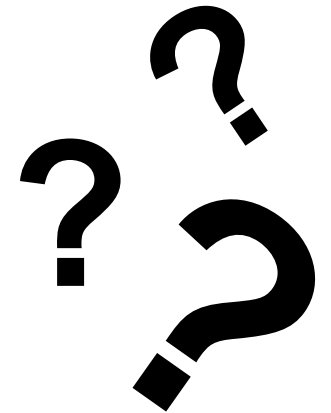




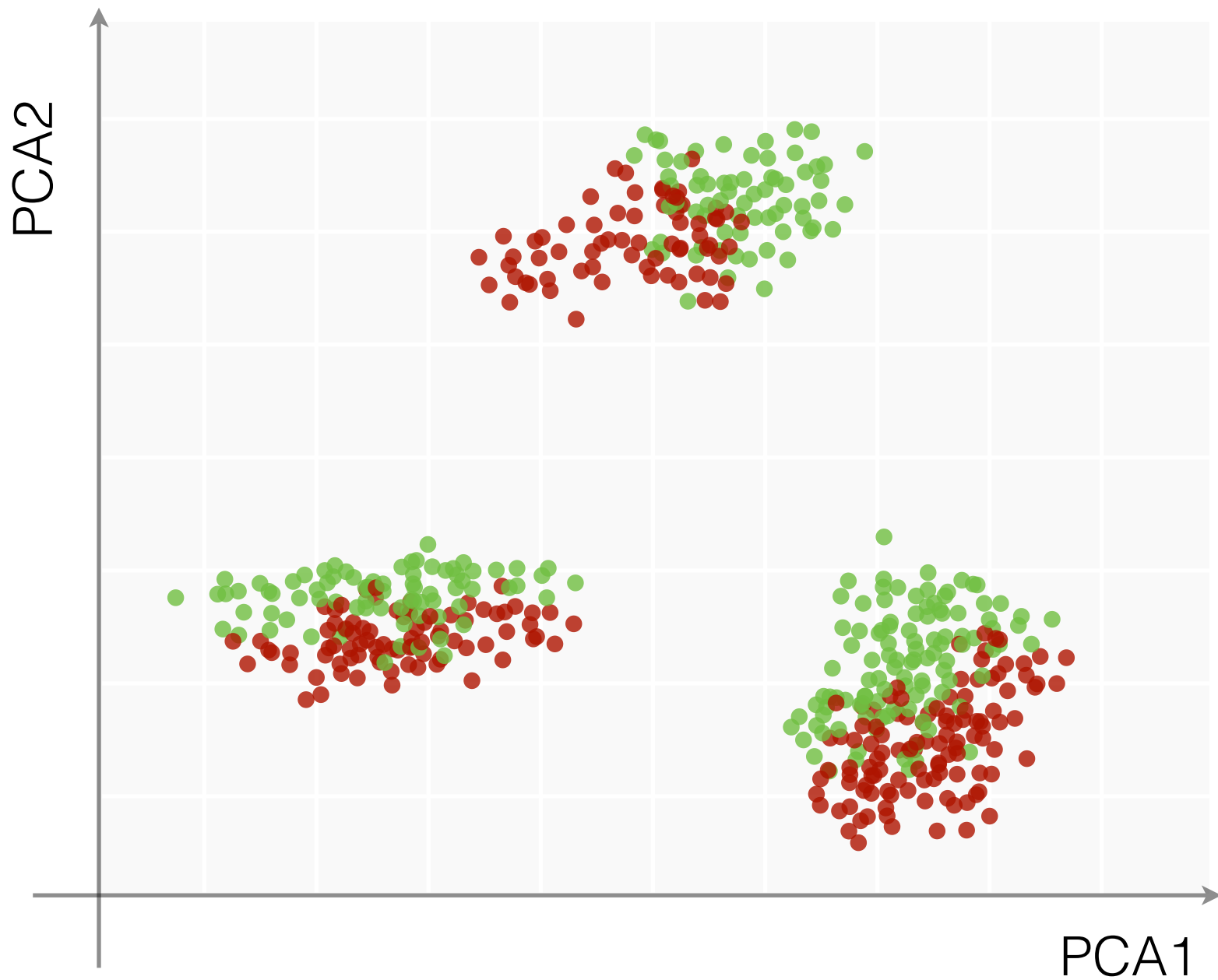
- HEALTHY
- DISEASE



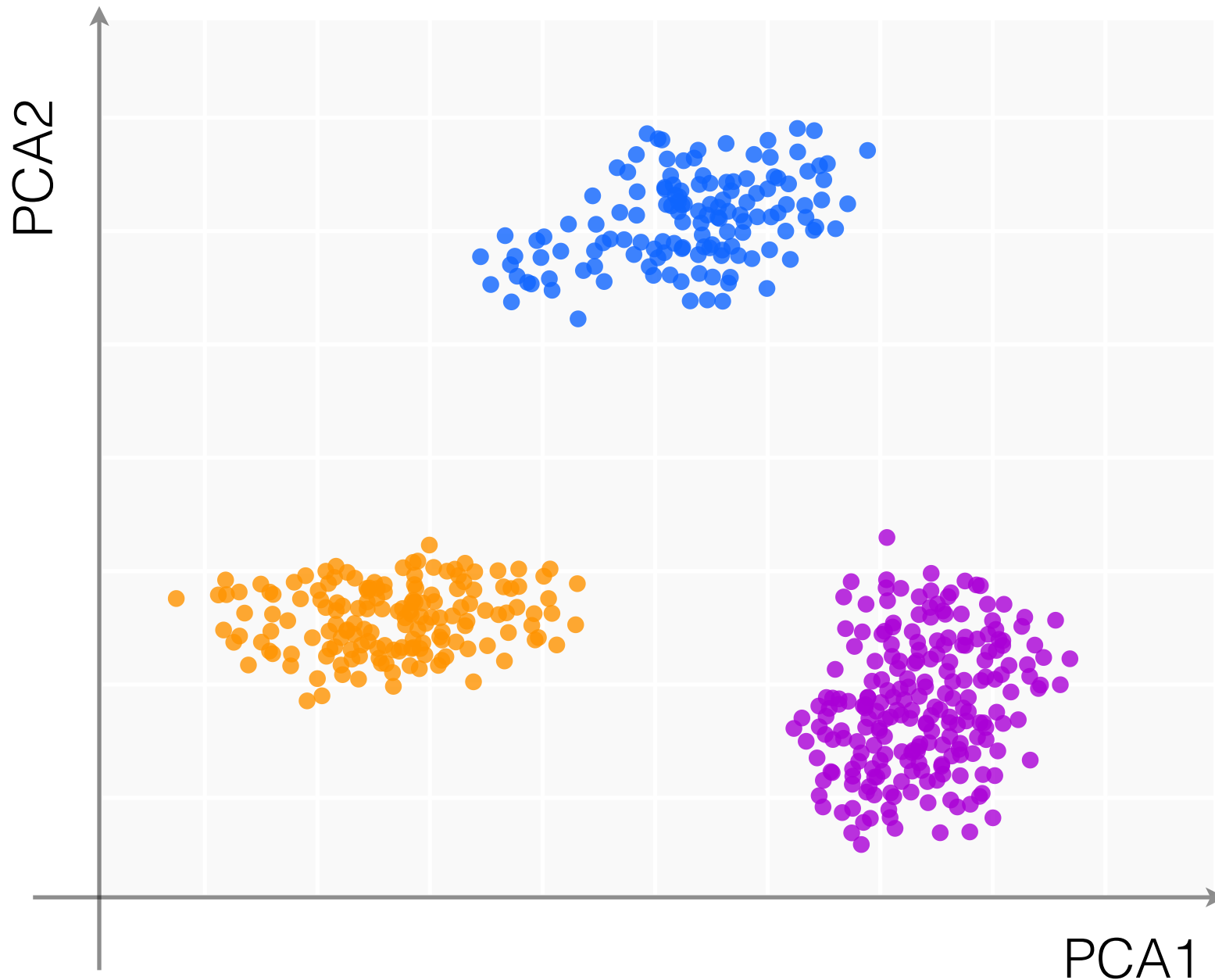
- HEALTHY
- DISEASE



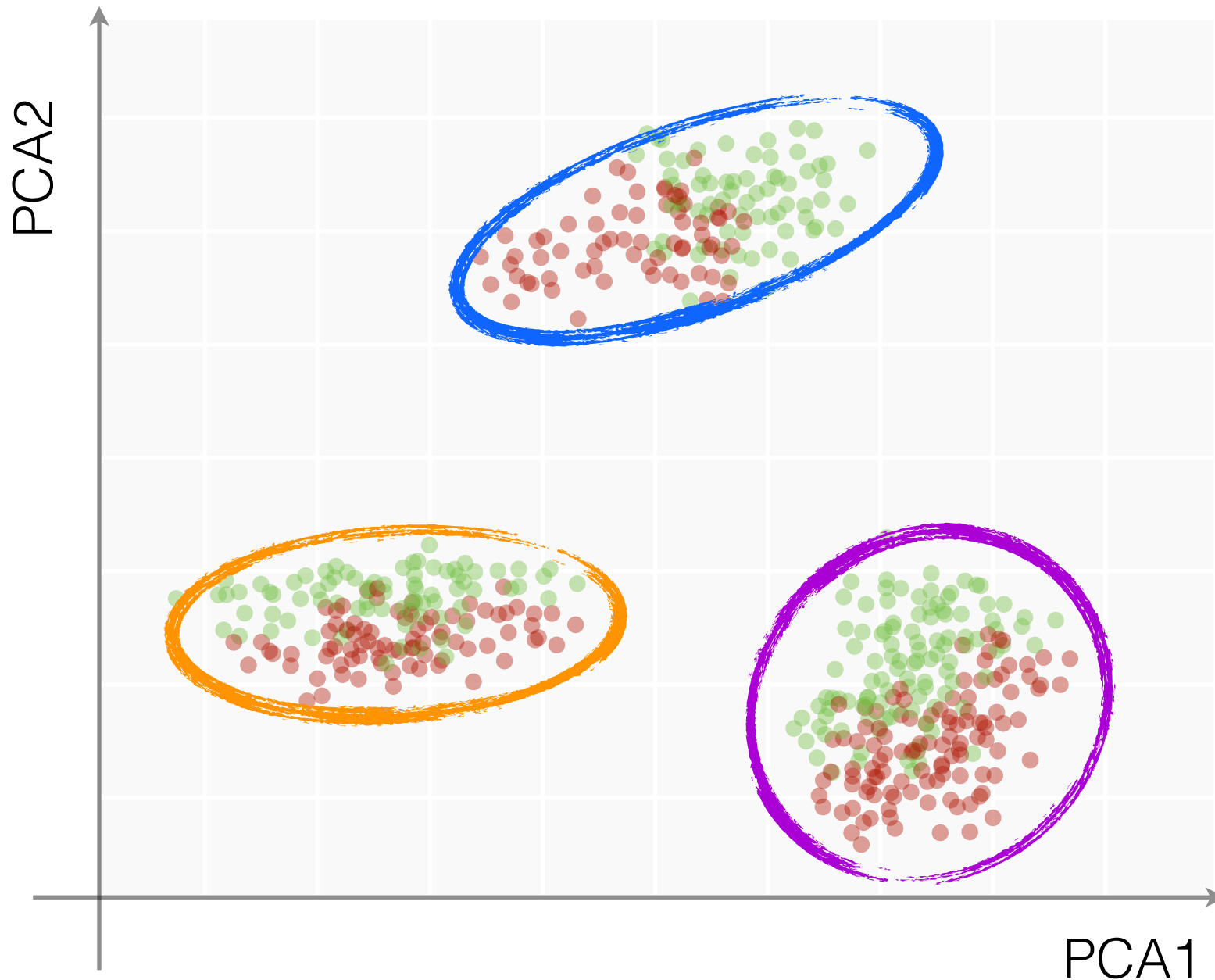




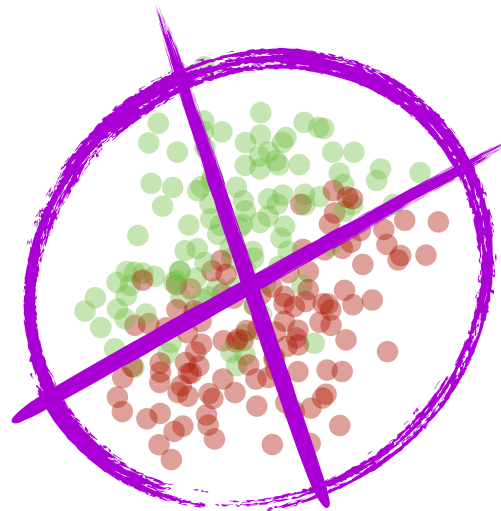
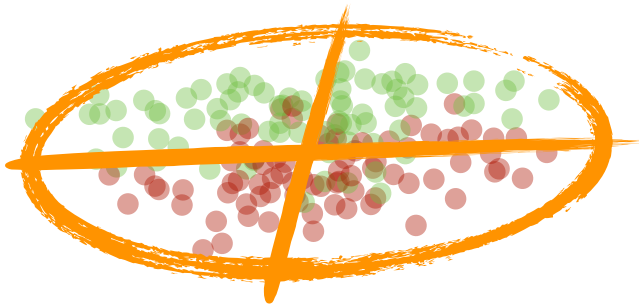
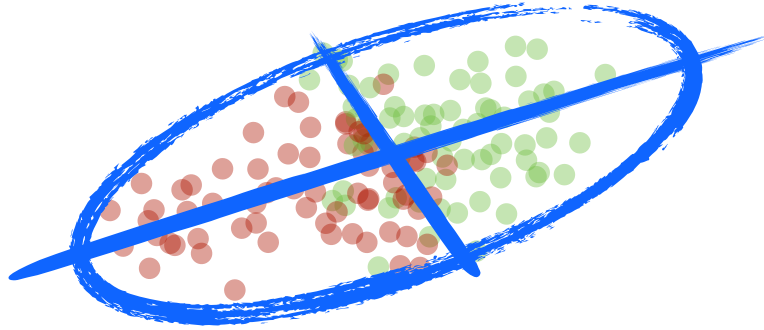
- HEALTHY
- DISEASE

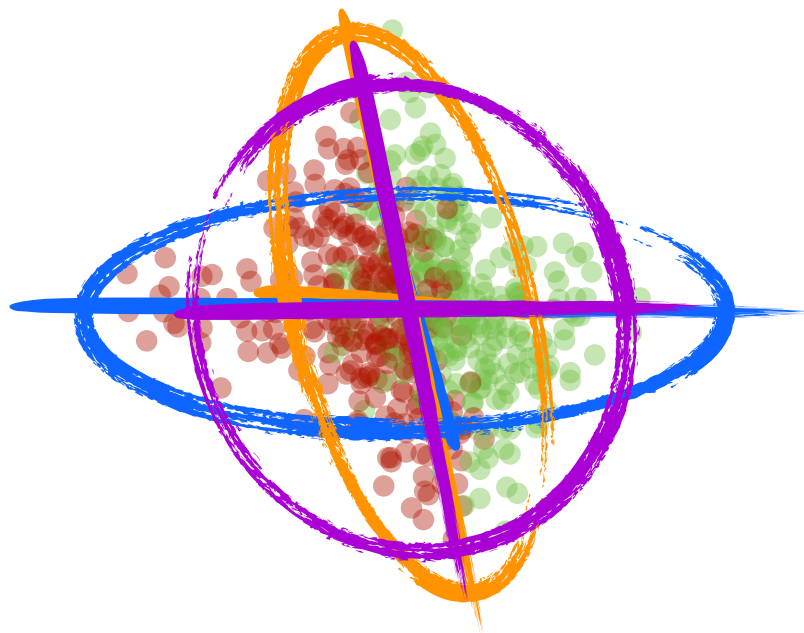


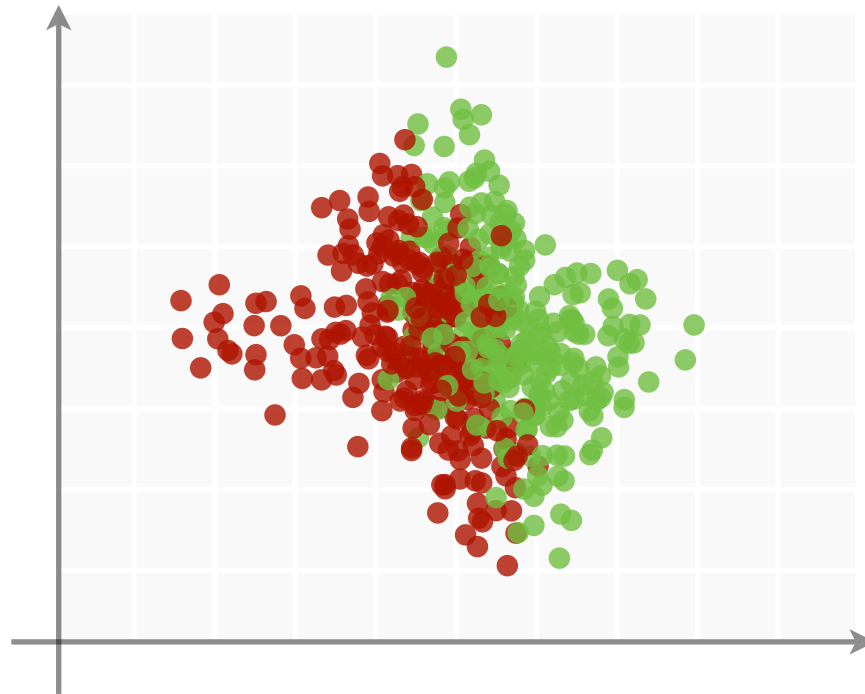
- BATCH 1
- BATCH 2
- BATCH 3

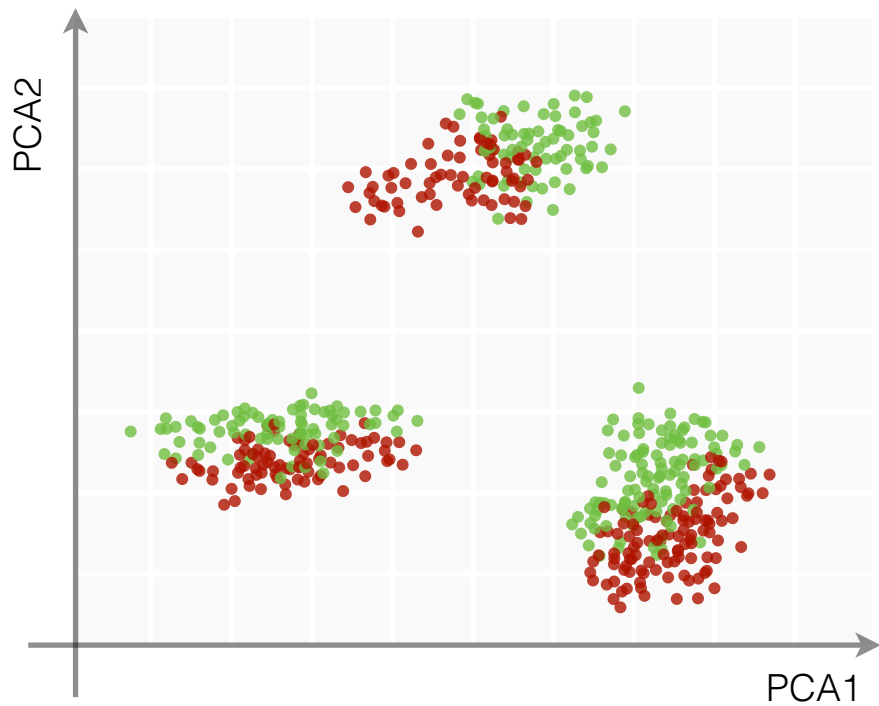


- HEALTHY
- DISEASE
- BATCH 1
- BATCH 2
- BATCH 3



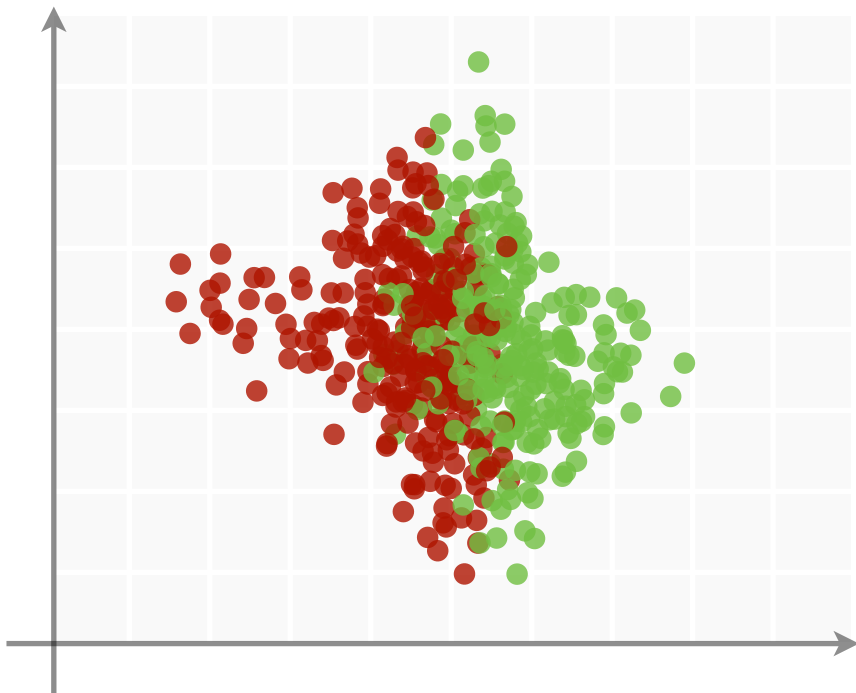




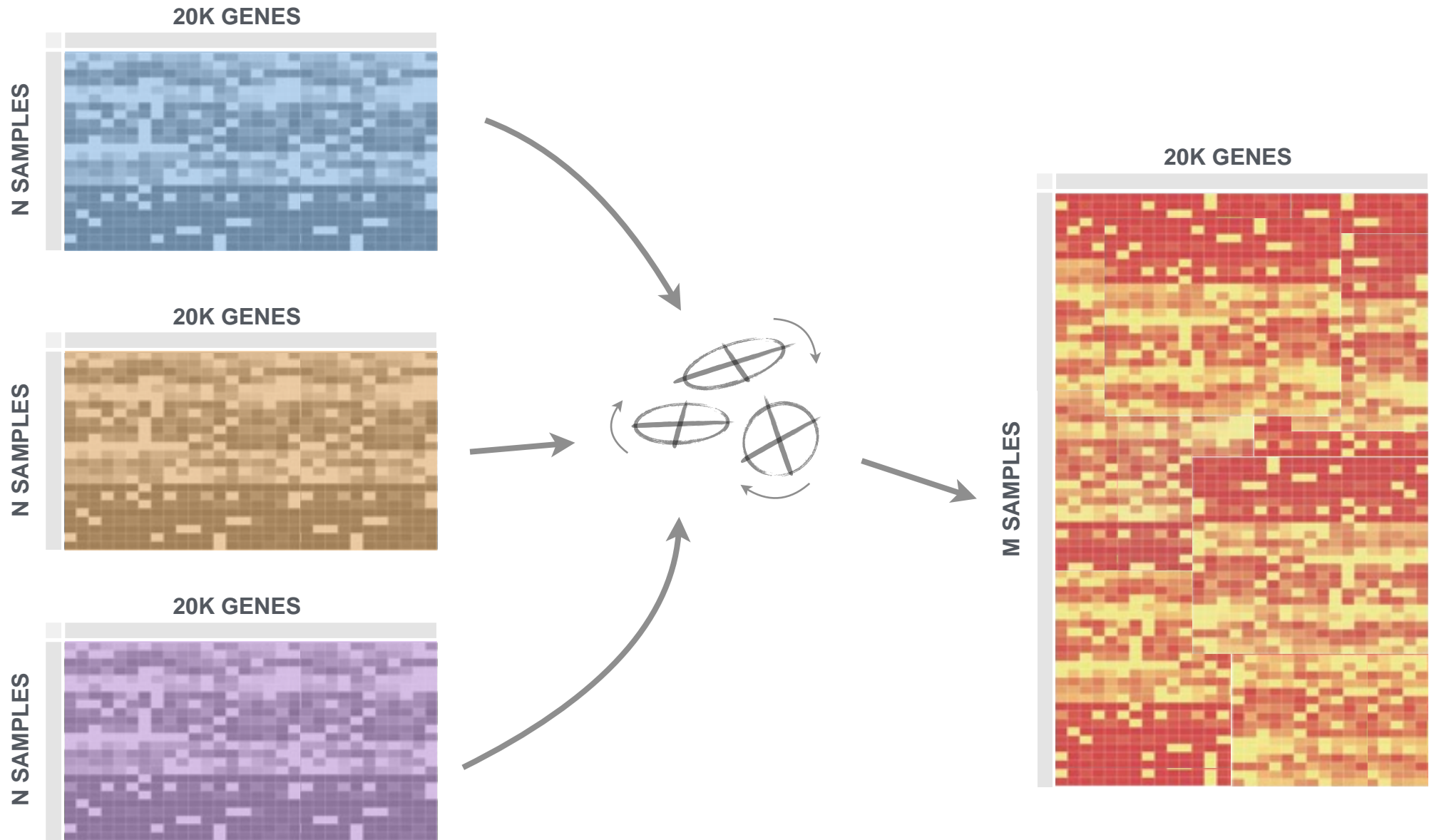


## Spectral Method for **Batch Effects** Removal

- completely automatic
- allows integration of public datasets
- merged data provides new insights

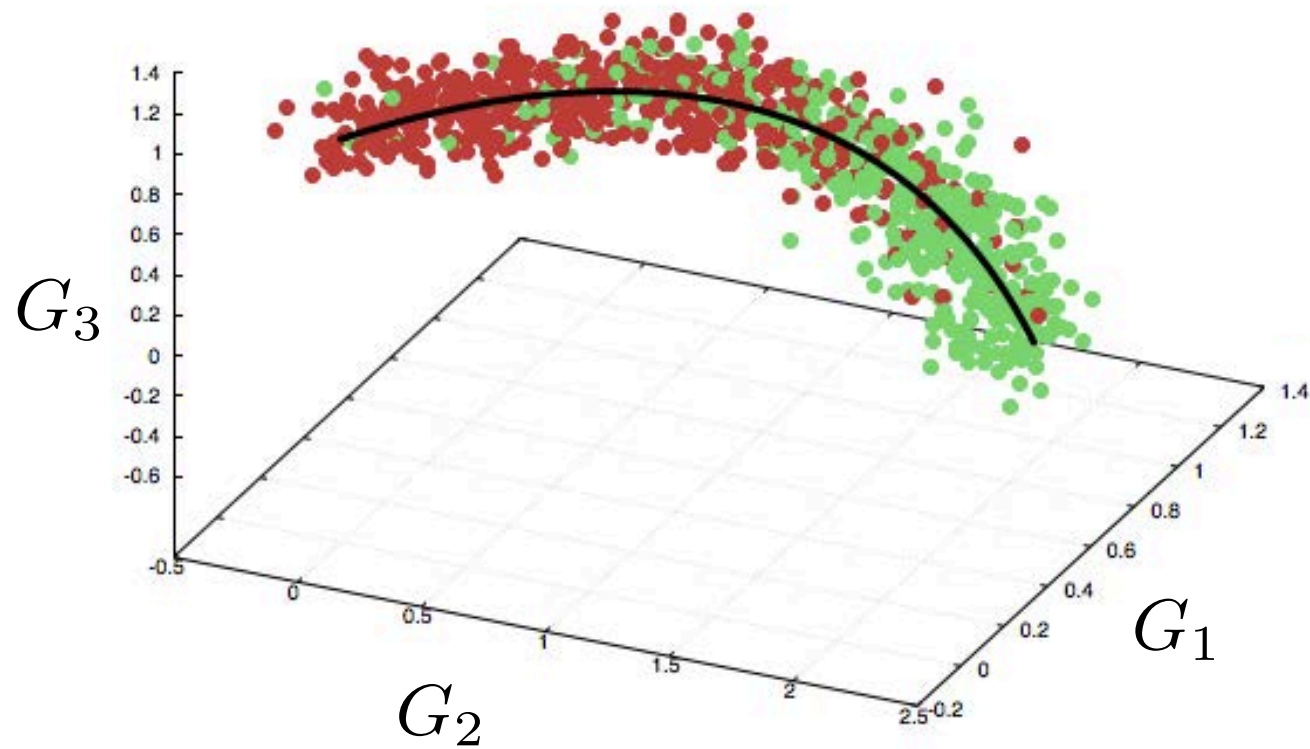


# DATA MERGING

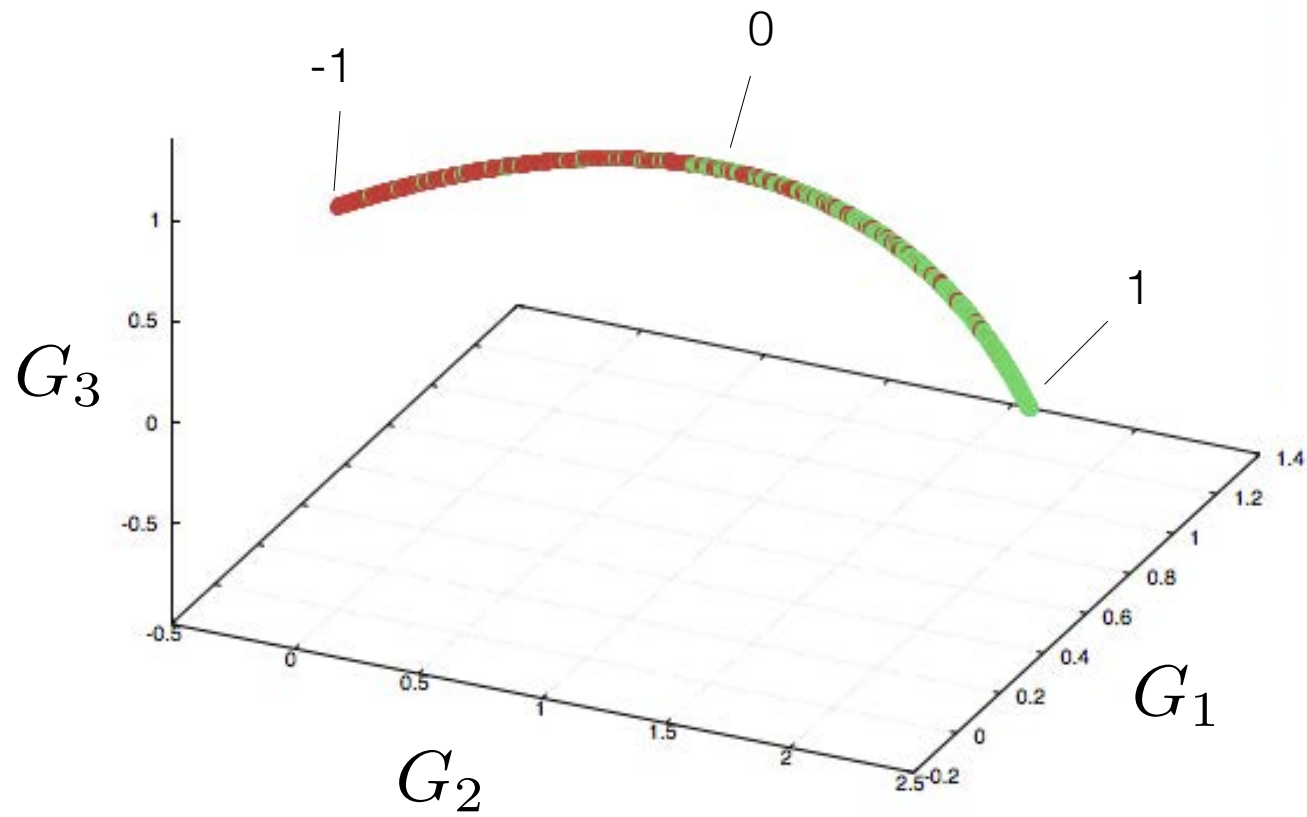




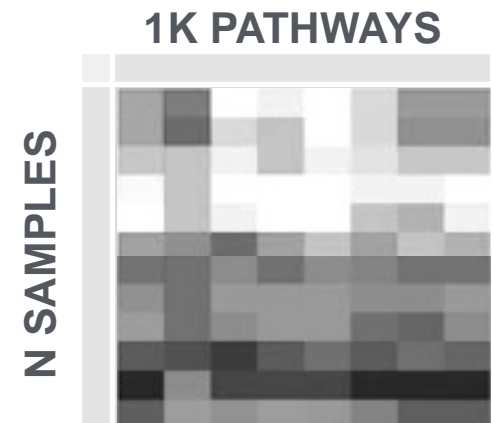
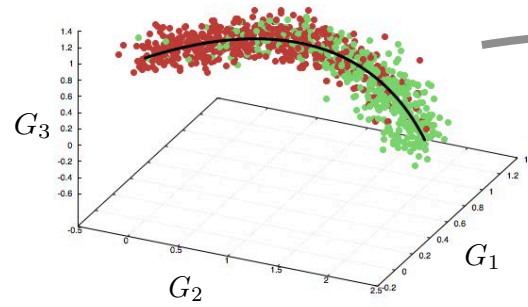
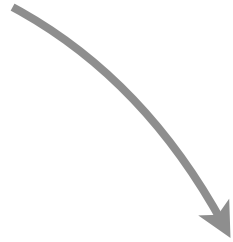
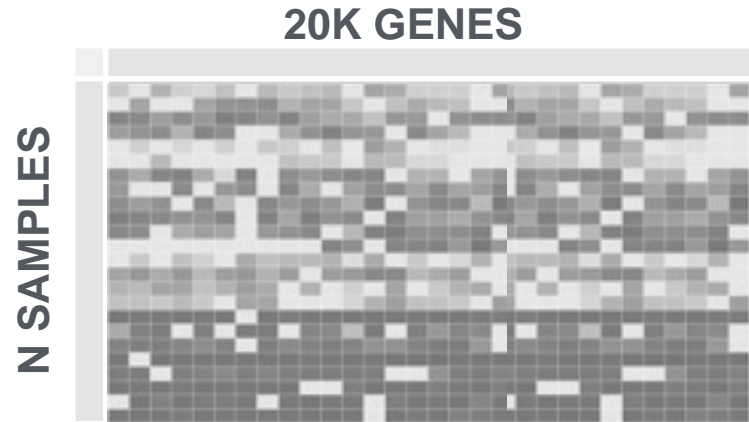
# PATHWAY DEREGULATION

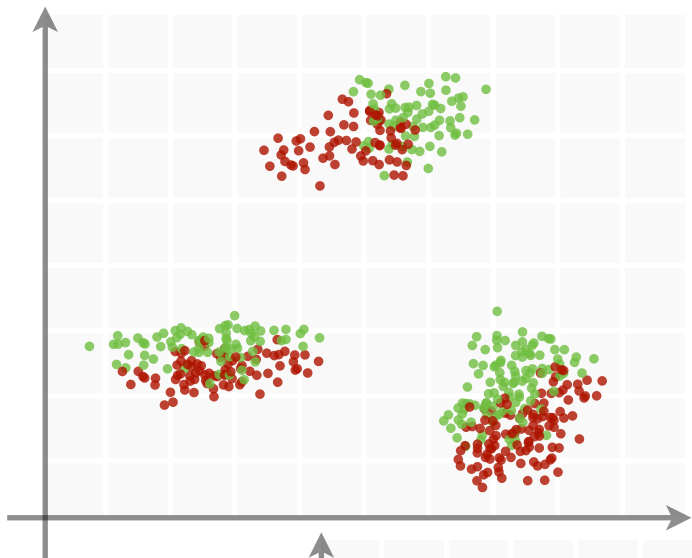


# PATHWAY DEREGULATION

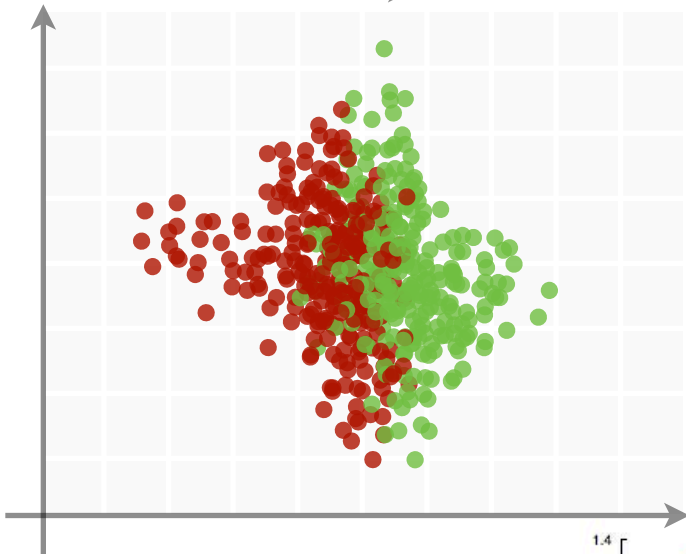


# PATHWAY DEREGULATION

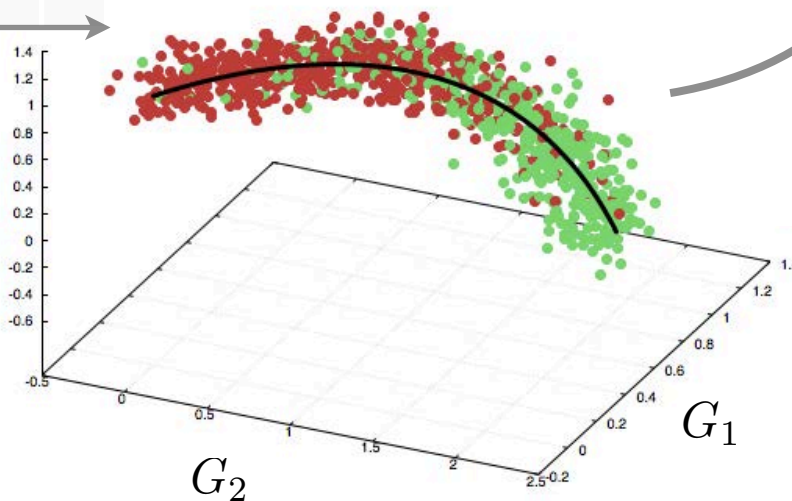




**Merge** lots  
of data



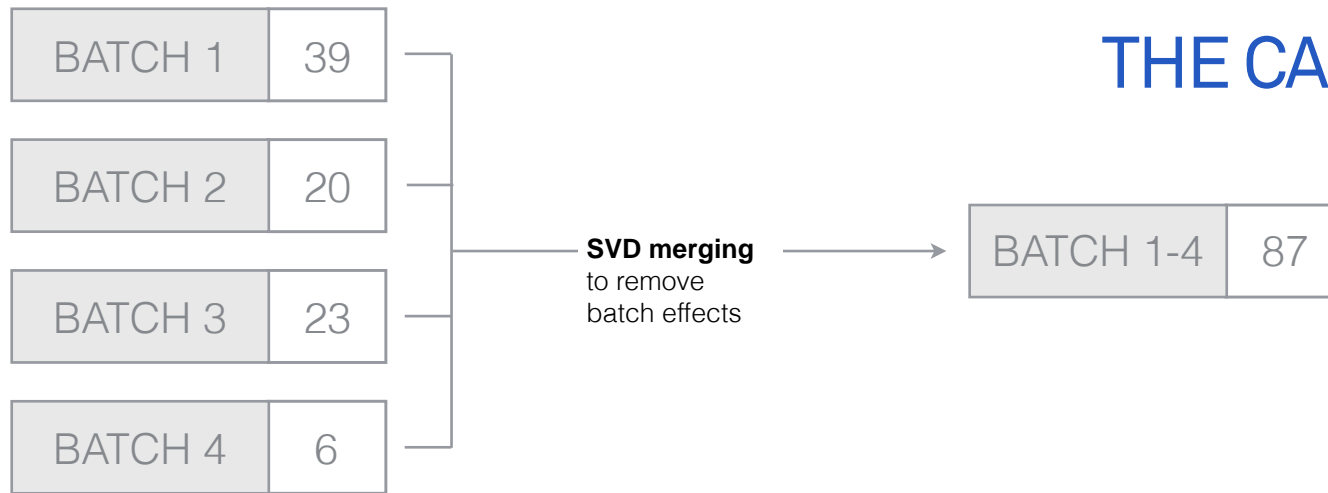
**Find** new  
deregulated  
pathways



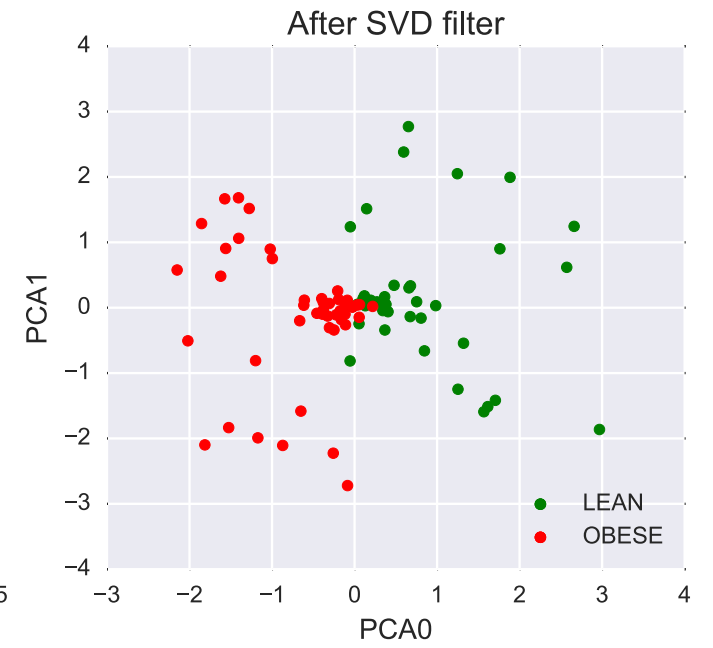
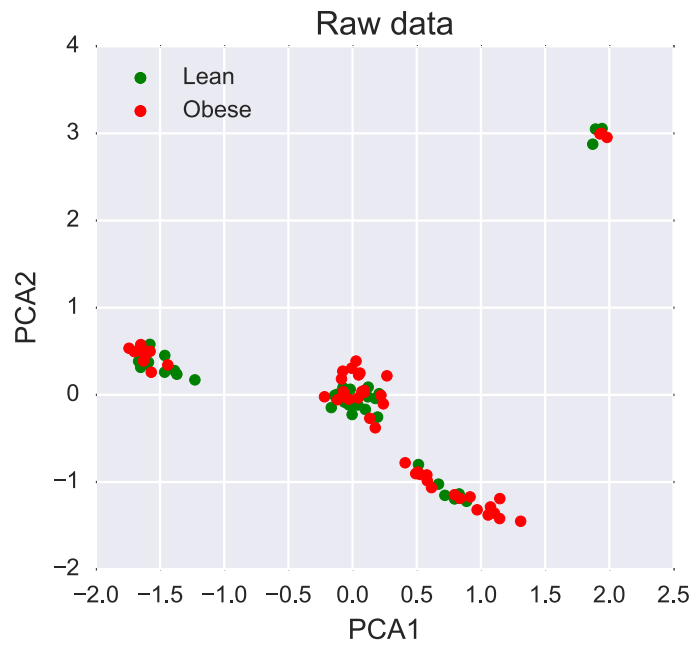
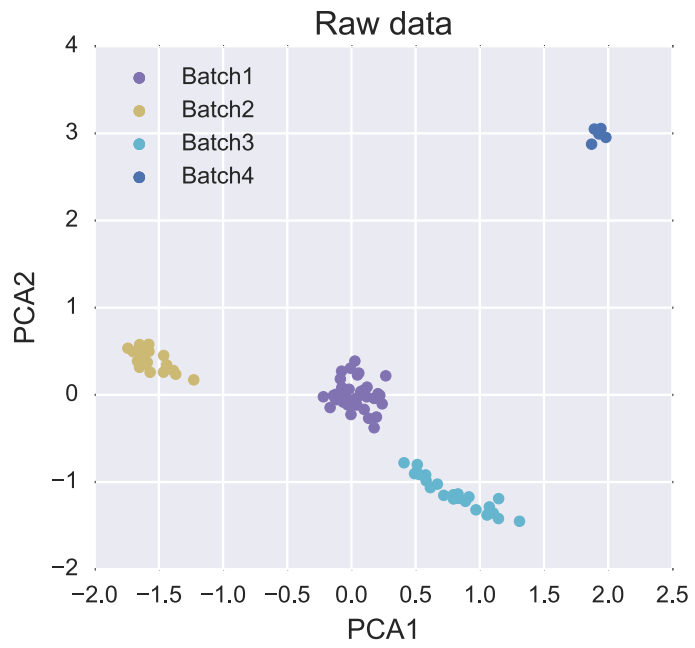
**Validate**  
in the lab



# THE CASE OF OBESITY

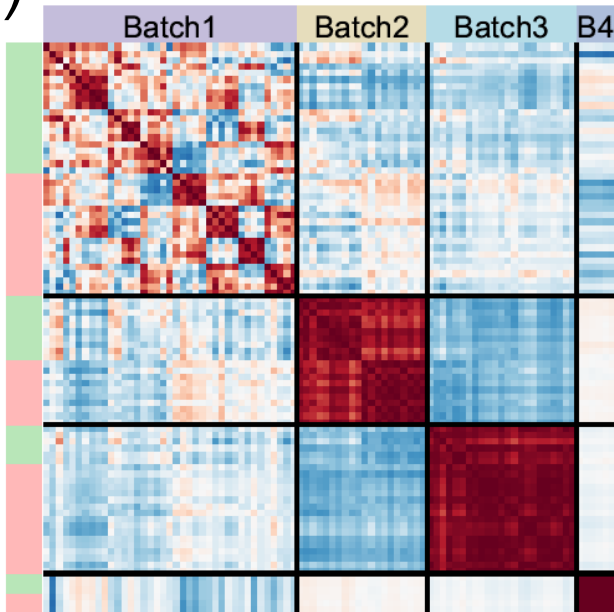


# FILTERING THE DATA

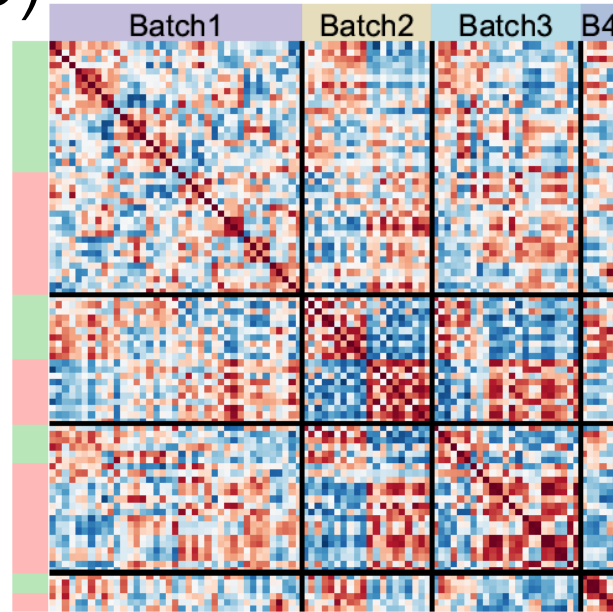


# FILTERING THE DATA

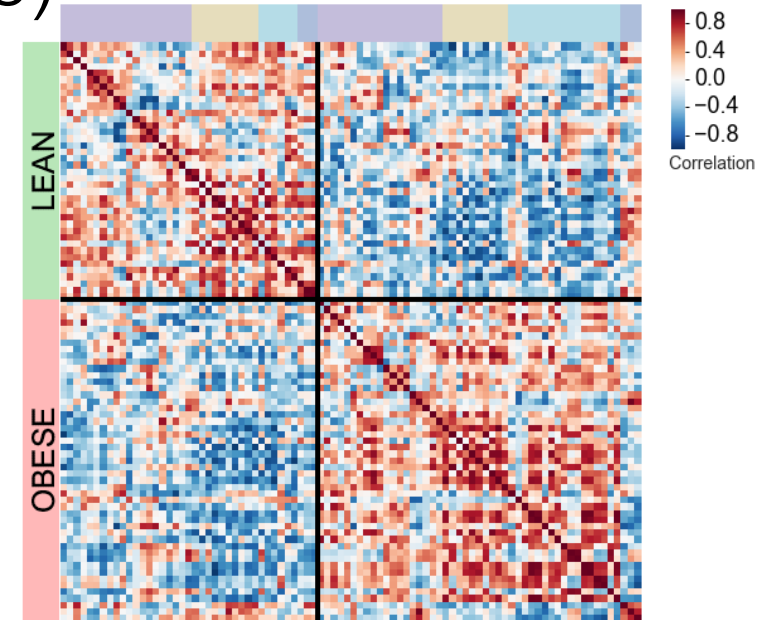
a)



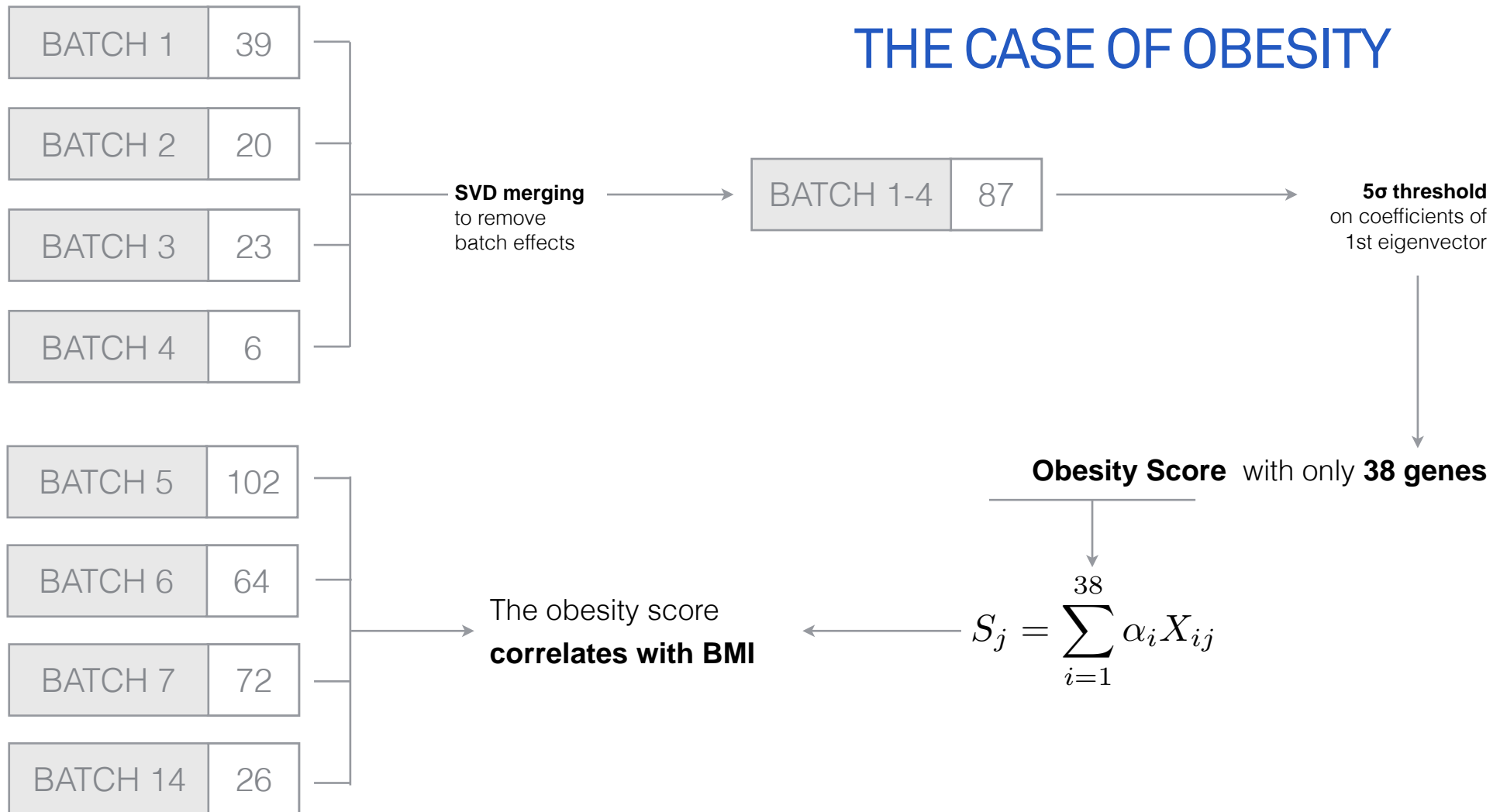
b)



c)



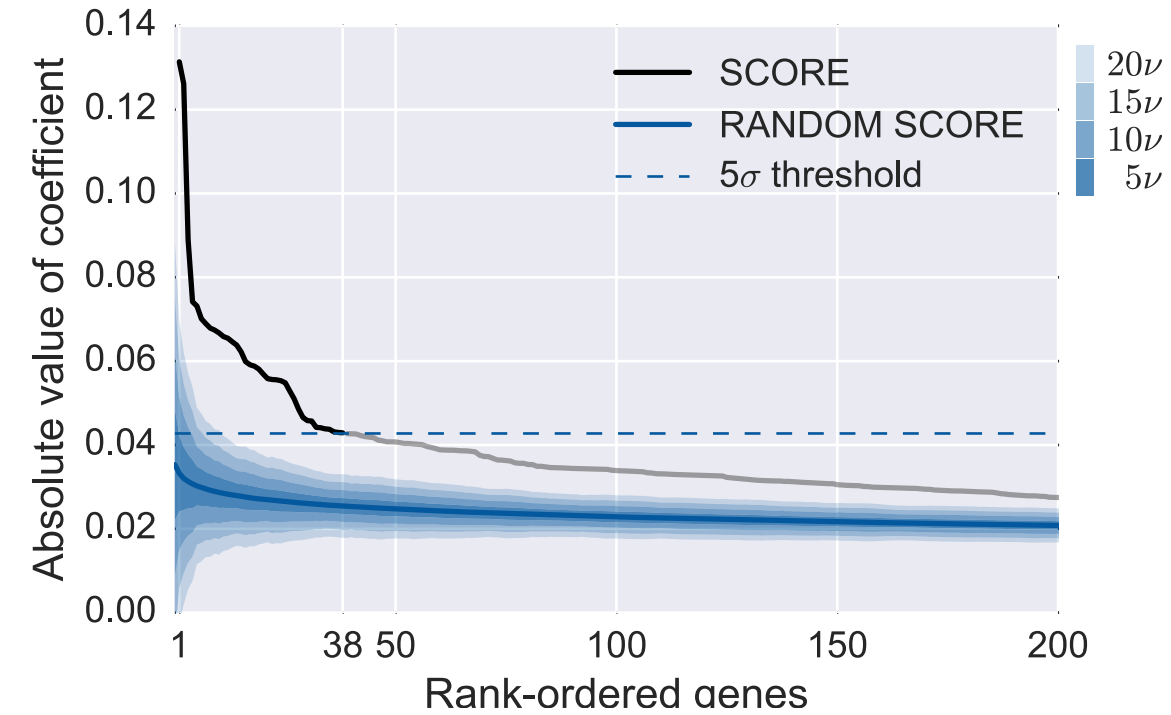
# THE CASE OF OBESITY



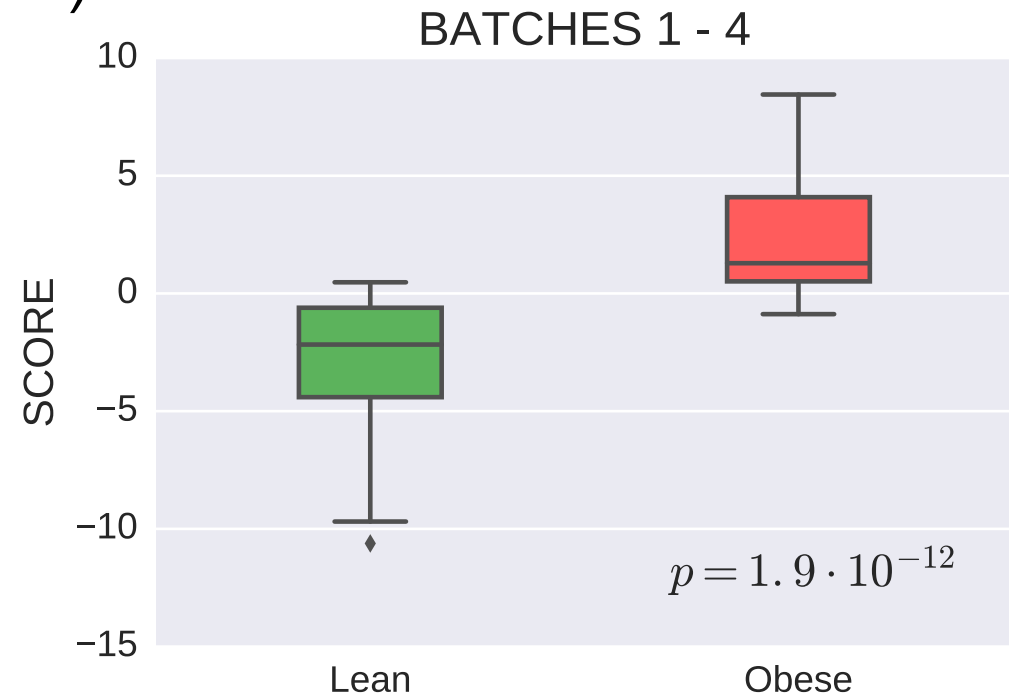


# THE OBESITY SCORE

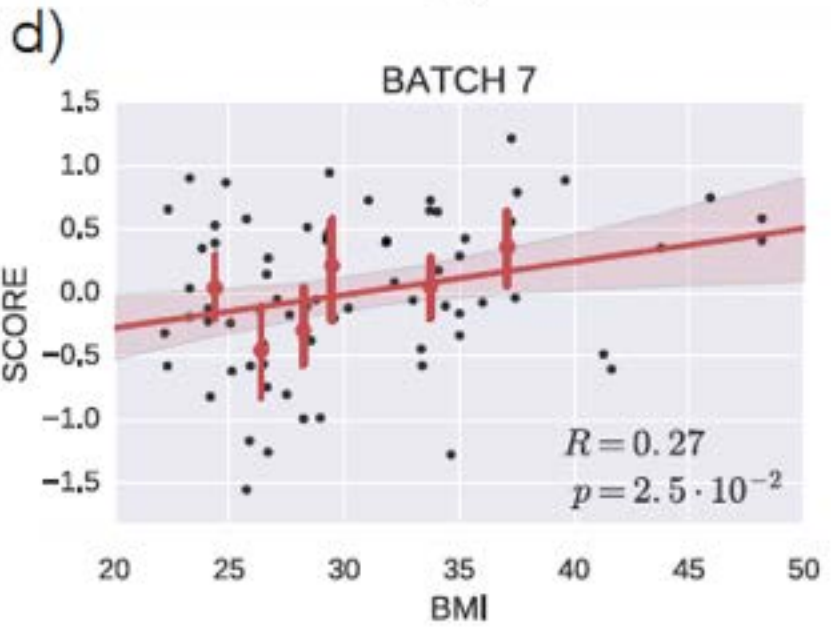
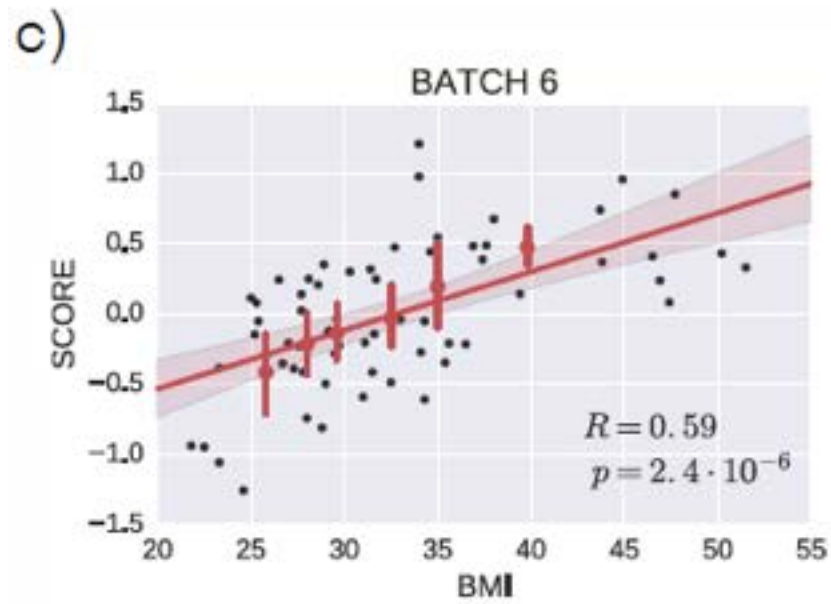
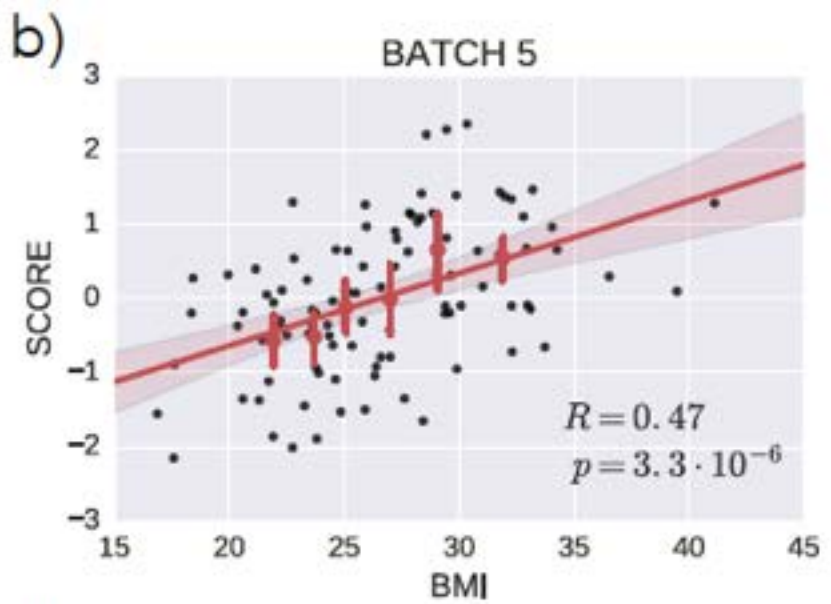
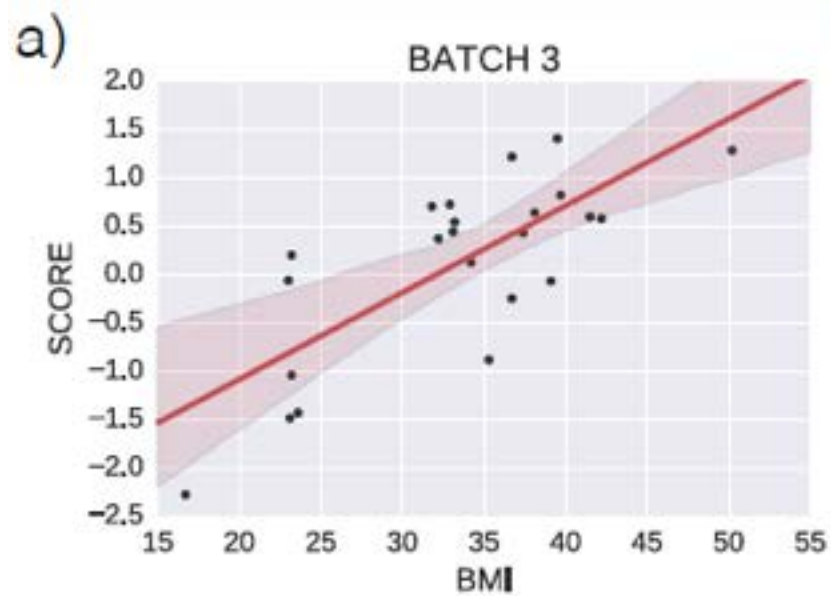
d)



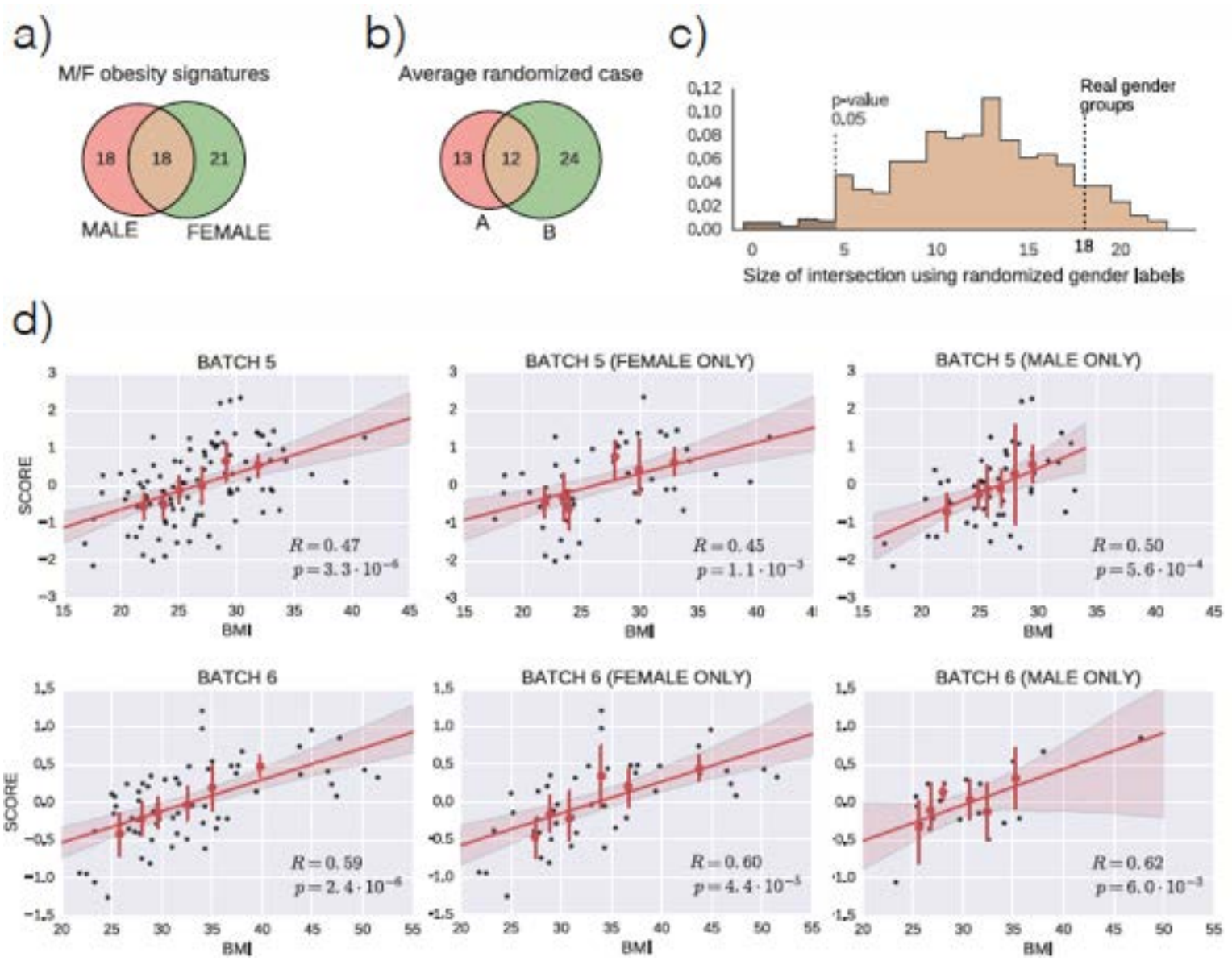
e)

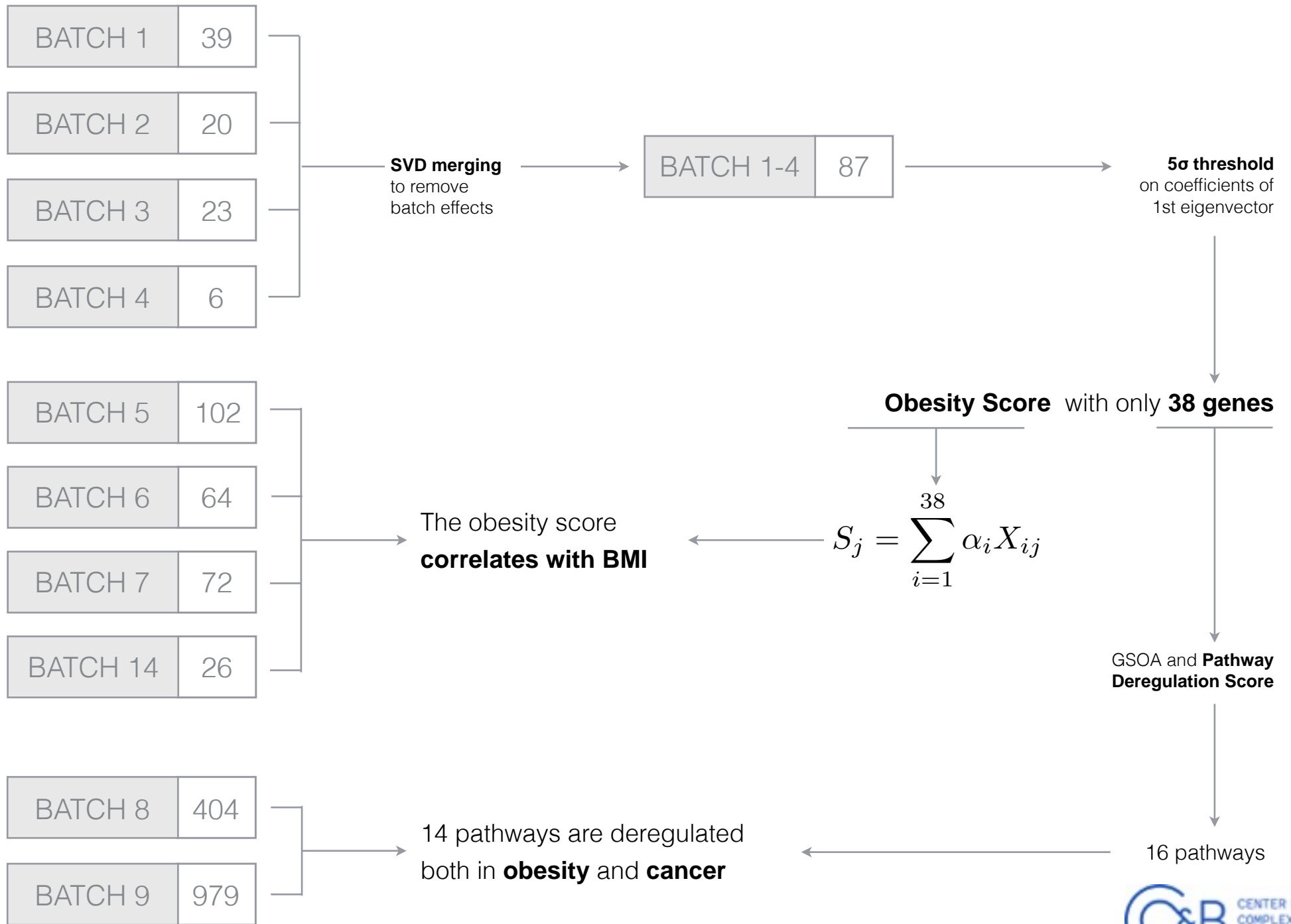


# SCORE CORRELATES WITH BMI

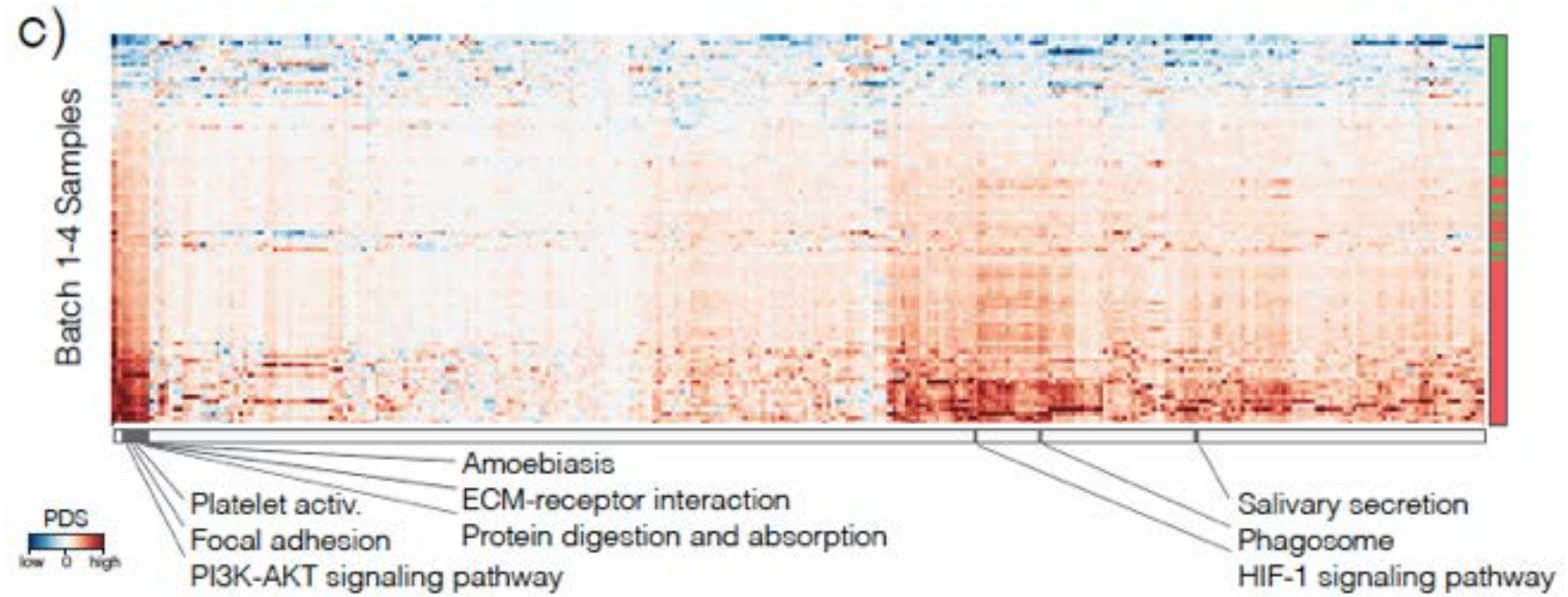
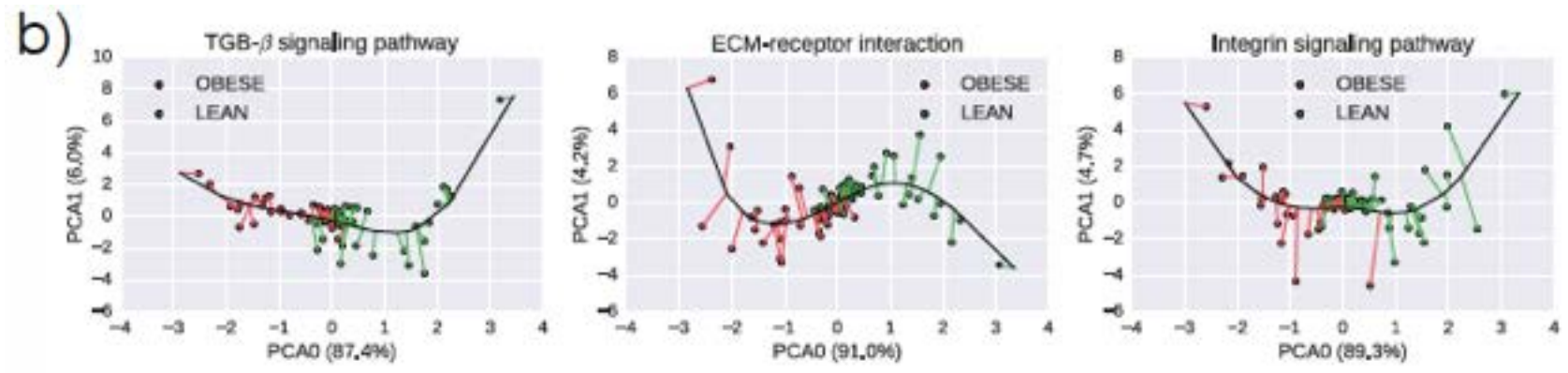


# SCORE IS GENDER INDEPENDENT





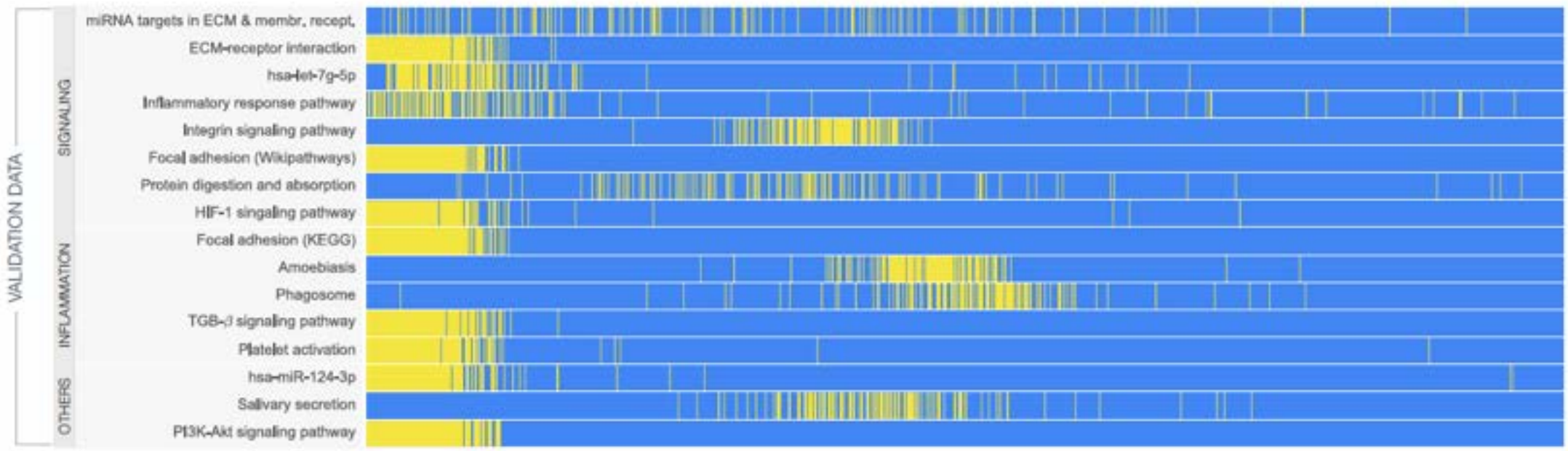
# PATHWAY DEREGULATION IN OBESITY



# PATHWAY DEREGULATION IN OBESITY AND CANCER

LEAN  
OBESE

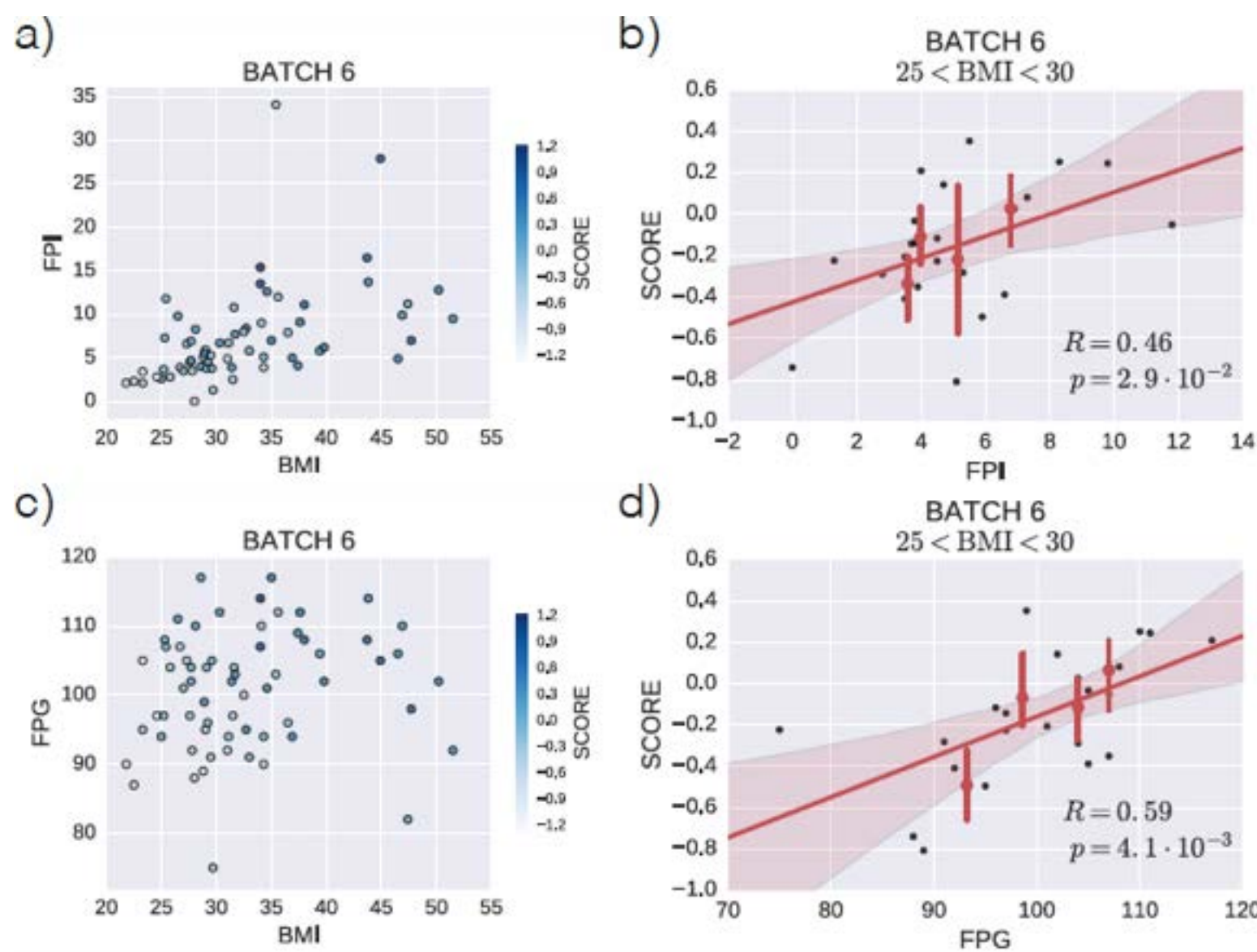
Batch 1-4 (samples sorted by PDS)



NORMAL  
TUMOR

Batch 9 (samples sorted by PDS)

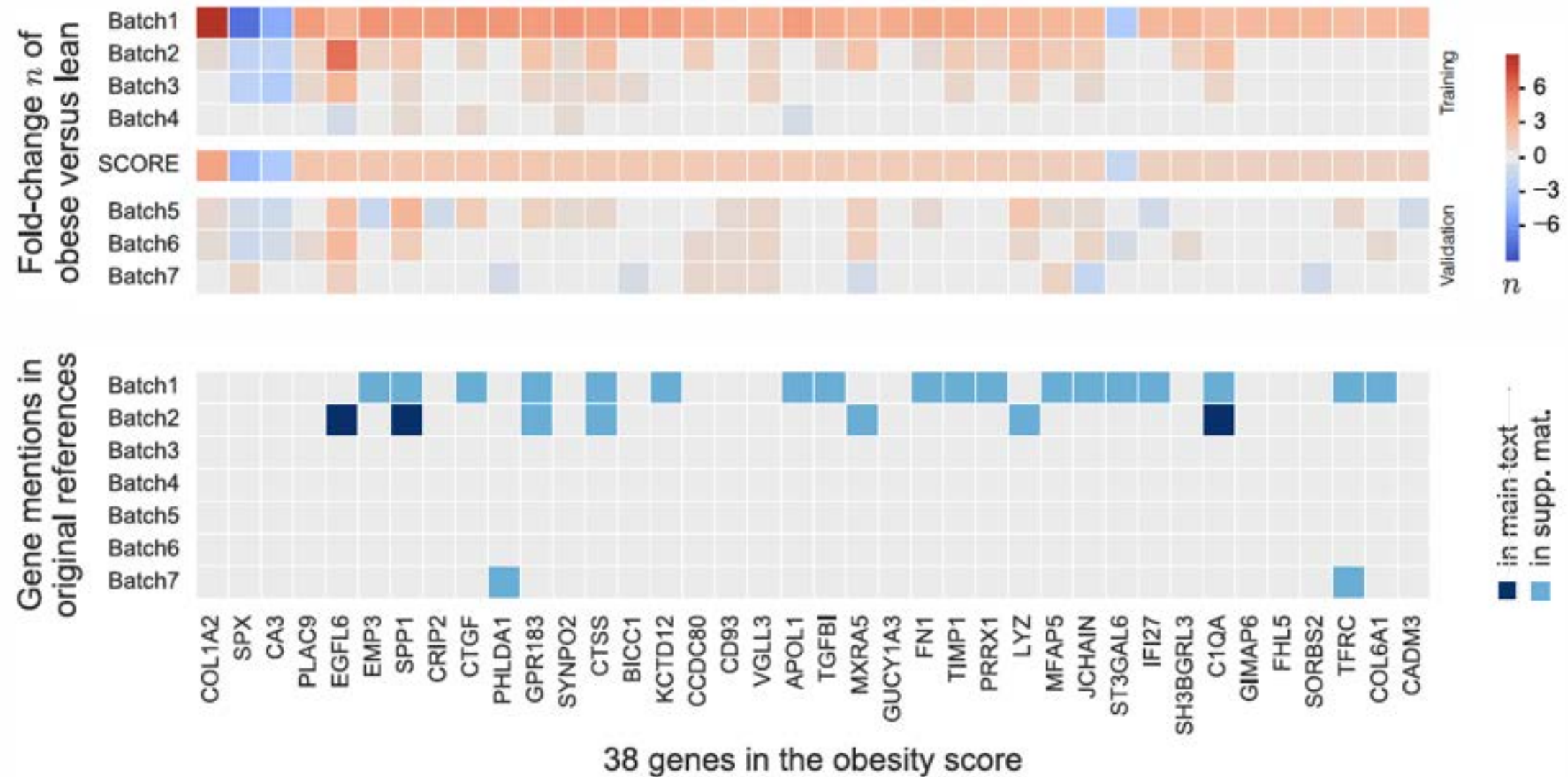
# OBESEITY SCORE AND TYPE II DIABETES



FPI: Fasting plasma insulin  
FPG: Fasting plasma glucose

# GENES IN THE OBESITY SIGNATURE

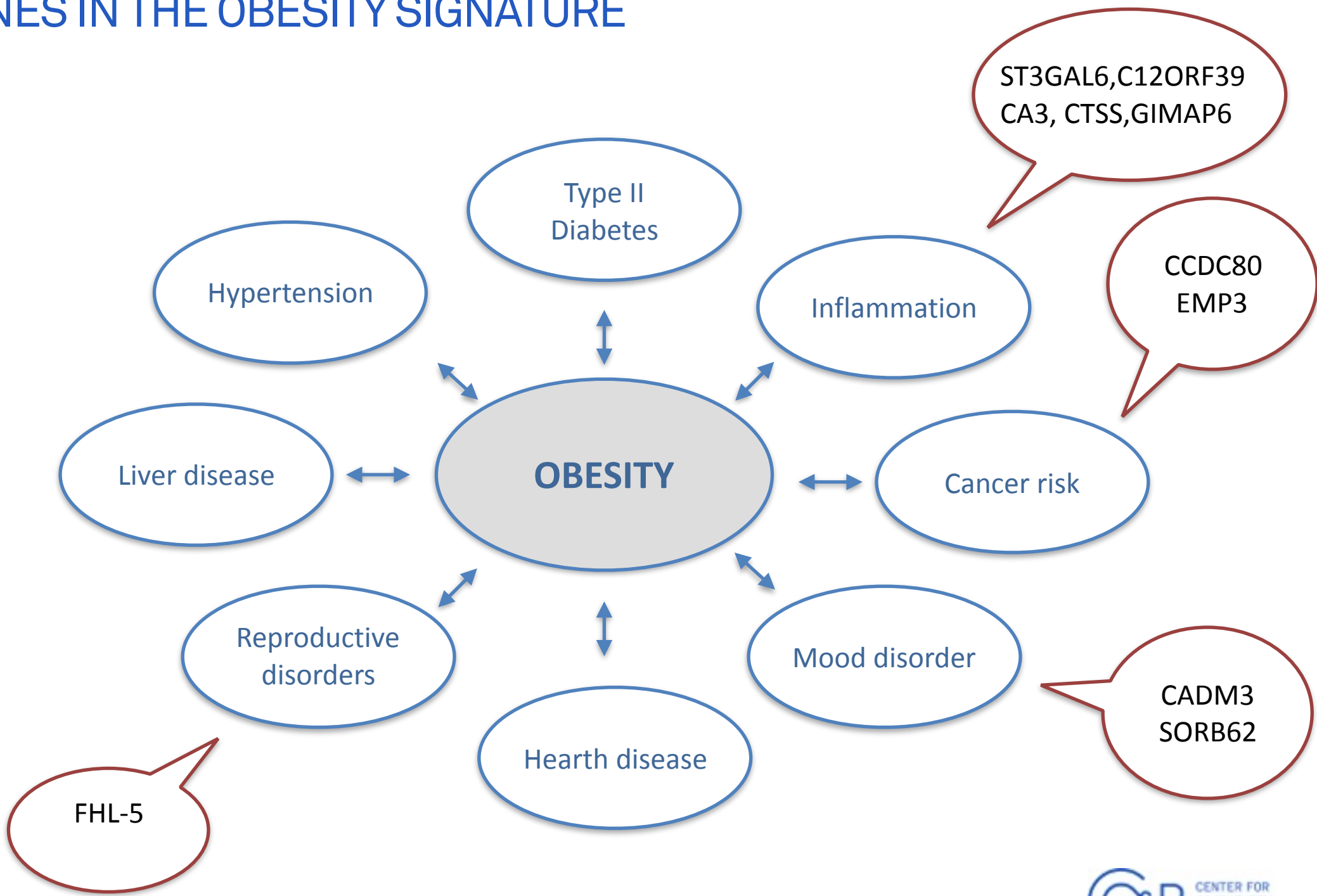
$5\sigma$  significance (like Higgs boson!)



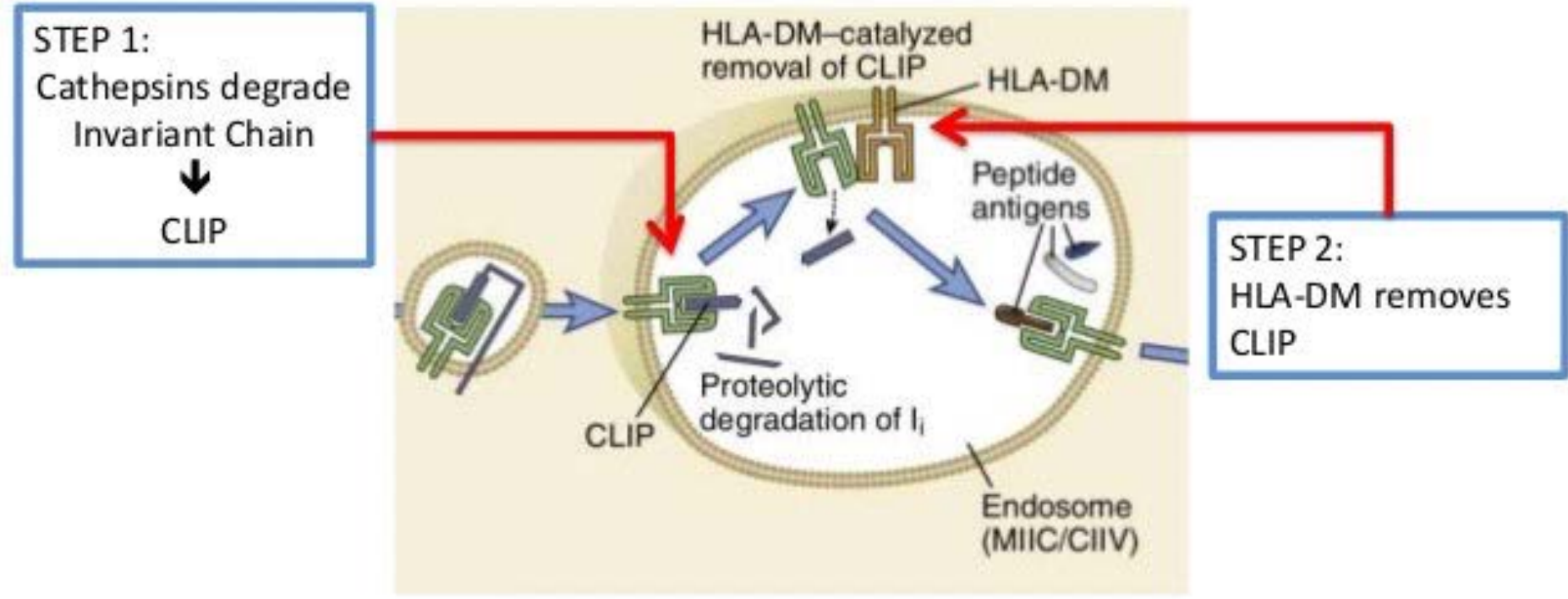
38 genes in the obesity score



# GENES IN THE OBESITY SIGNATURE



# Class II MHC Pathway

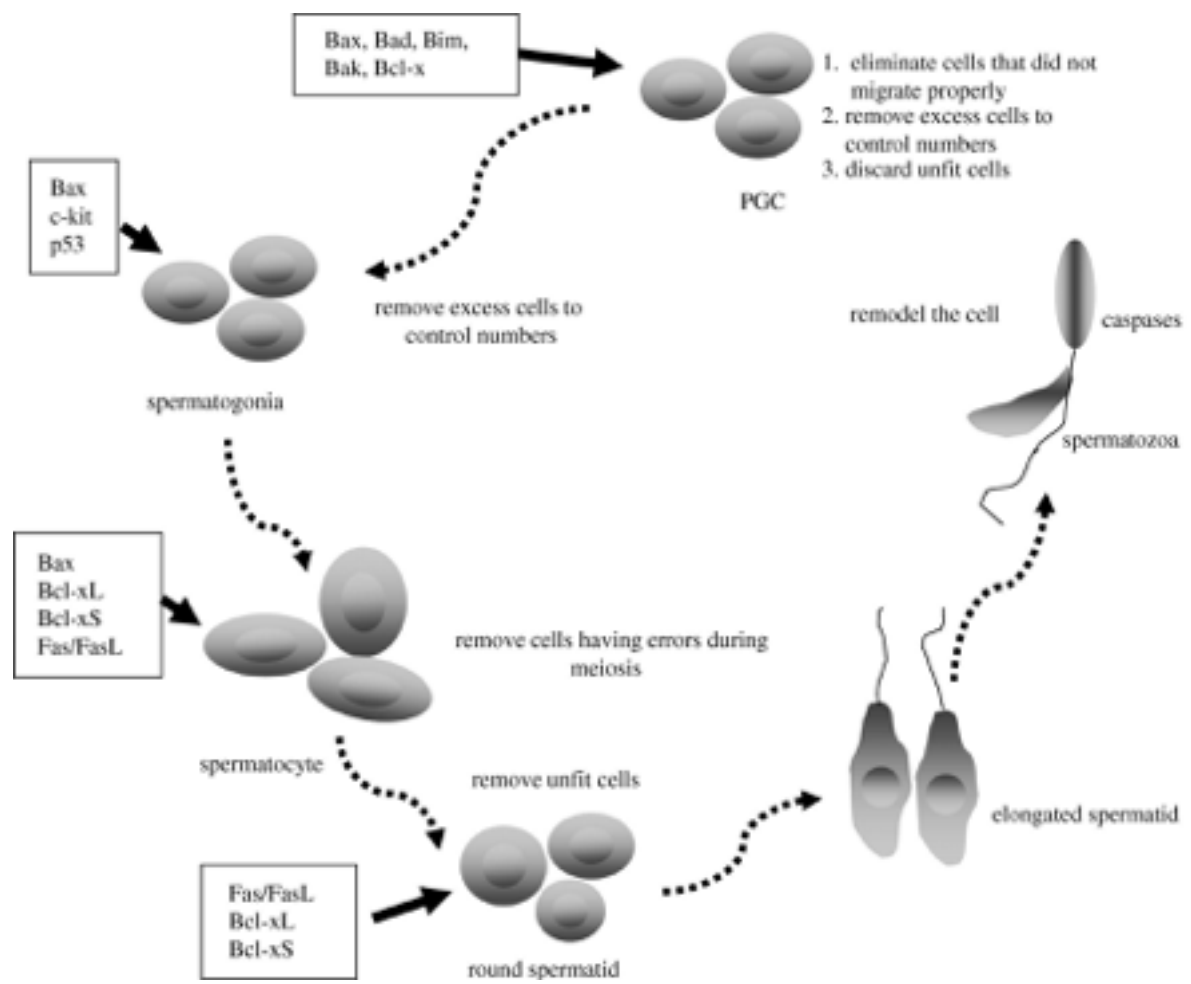
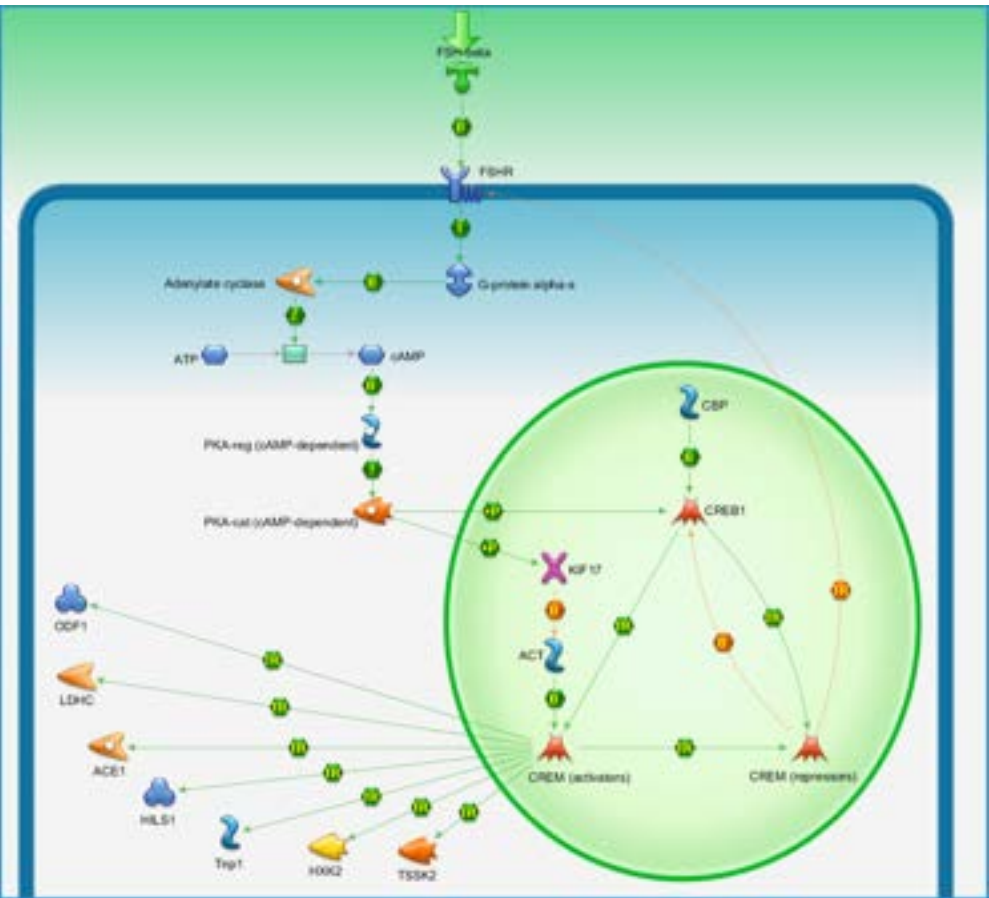


Cellular and Molecular Immunology 8<sup>th</sup> Ed. (2015) by Abbas et al.

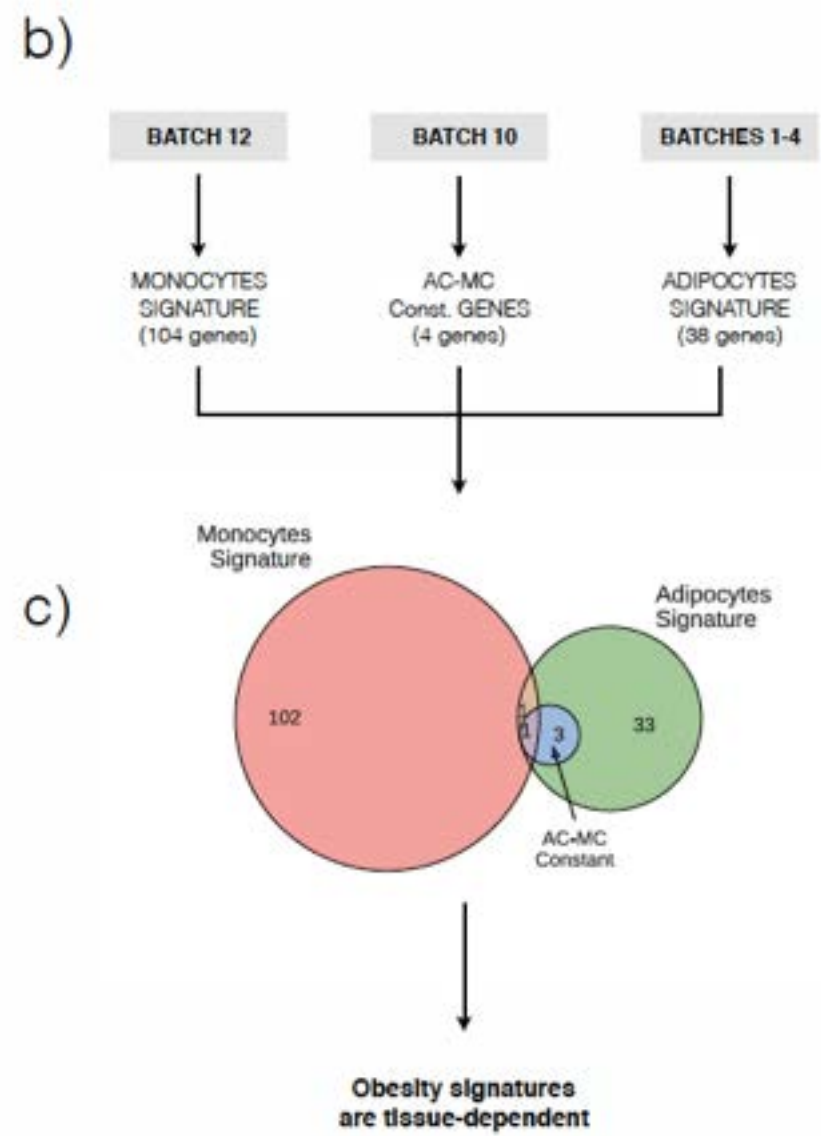
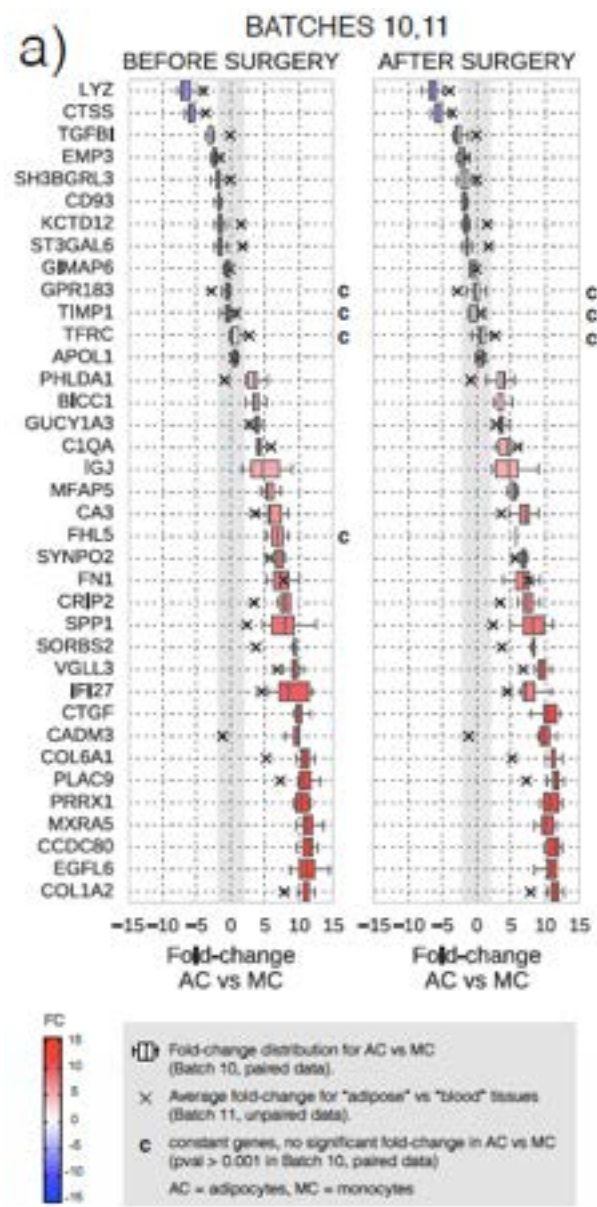
Cathepsins S circulating levels have been found to correlate with BMI and triglycerides

# GENES IN THE OBESITY SIGNATURE: FERTILITY

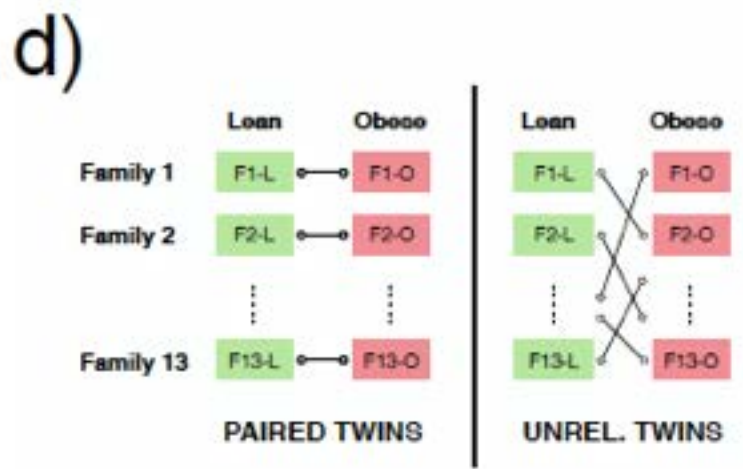
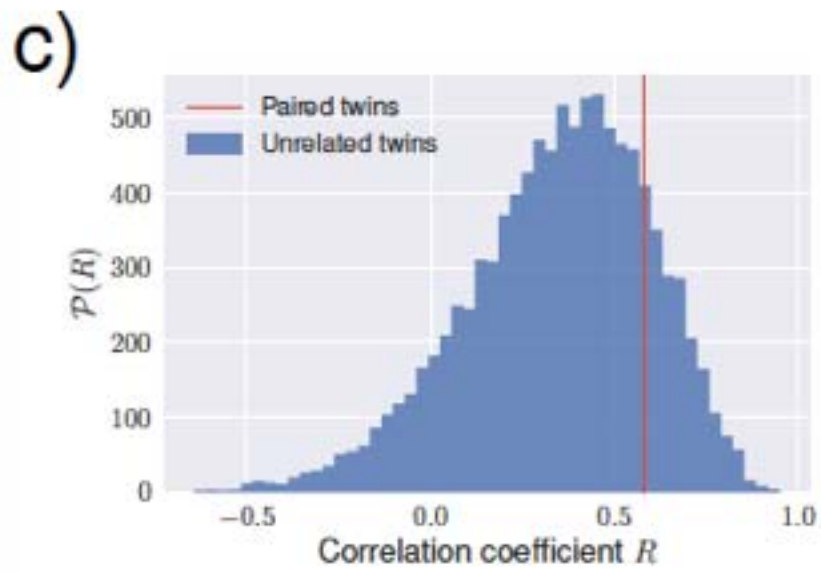
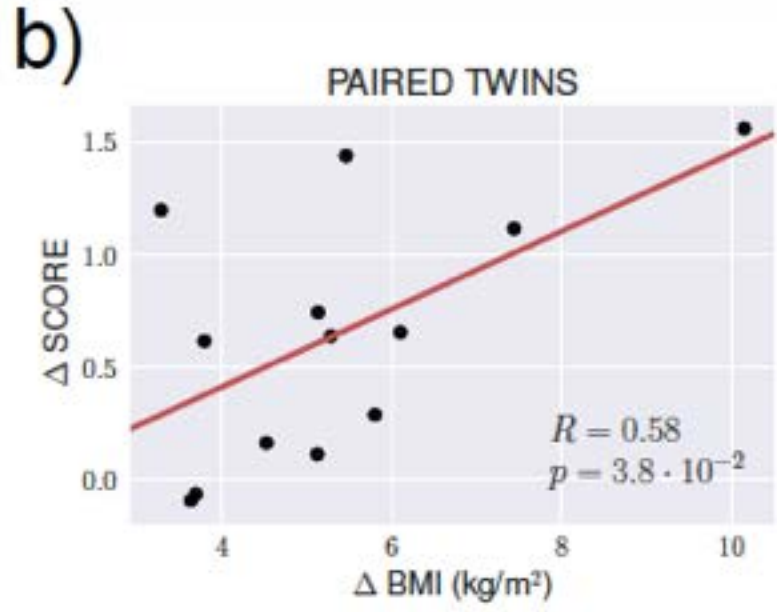
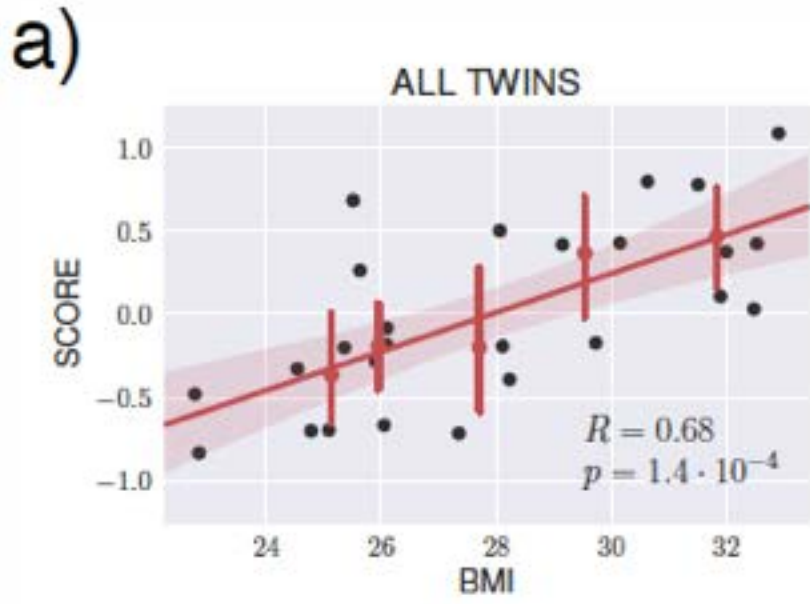
## FHL5



# SIGNATURE IN MONOCYTES



# IS OBESITY A GENETIC DISEASE?



# CONCLUSIONS

Obesity is not a gender dependent disease

Genetic causes of obesity are extremely rare

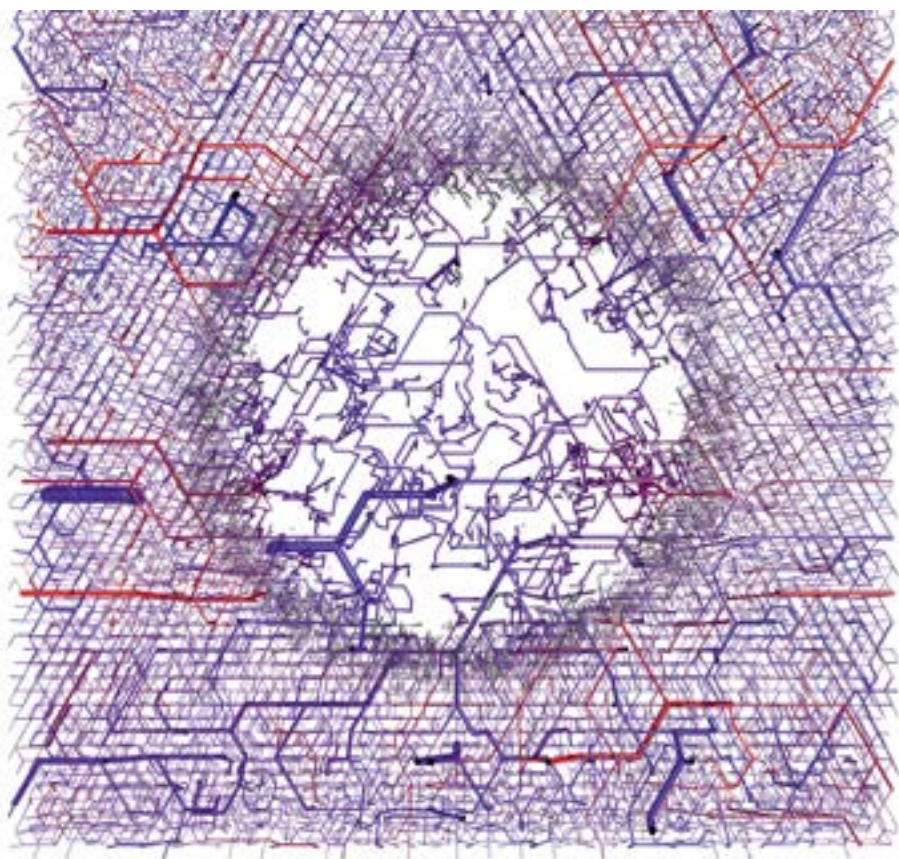
Gene expression data, once properly filtered, help identify a fingerprint of obesity.

Environment and lifestyle are the keys!

# THE GROUP

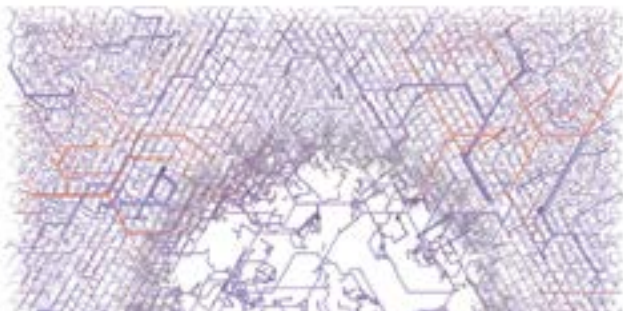


2016-2017



Caterina La Porta and Stefano Zapperi

# The Physics of Cancer



Publisher: Cambridge University Press

Publication date: May 2017

ISBN: 9781316271759

DOI: 10.1017/9781316271759



Thank you for your attention!