Wrocław University of Science and Technology

"Exploratory data analysis of a clinical study group - revealing patient subgroups"

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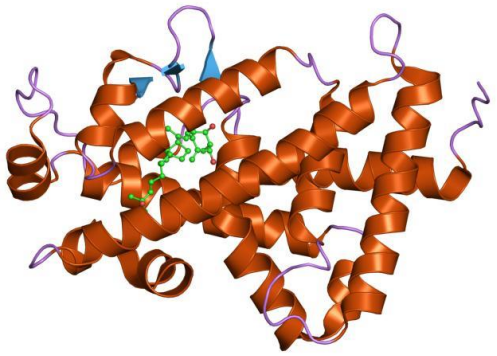
Assessing the influence of Vitamin D Receptor gene polymorphisms („changes” in DNA)

(Lukasz Laczmanski Ph.D., D. Sc. , Wroclaw Medical University)

UMW

Vitamin D Receptor



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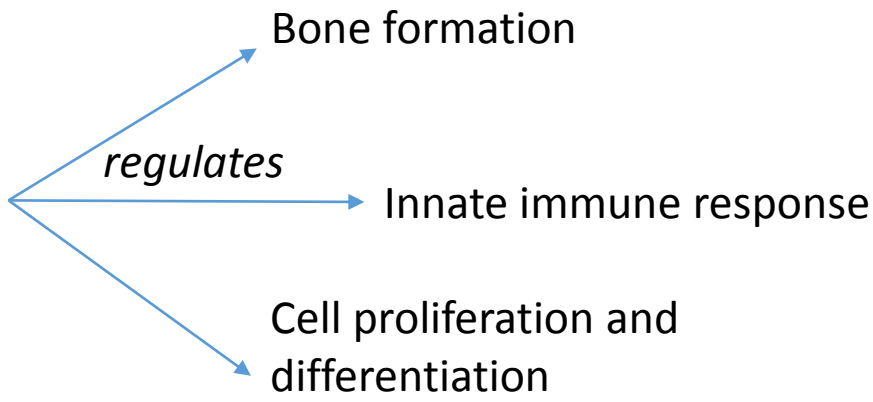

- Our research hypothesis:
  - VDR polymorphisms influence sex hormone blood levels
- The plan:
  - **Explore gathered clinical data**
  - Build regression models relating VDR polymorphisms and blood levels of sex hormones

Dataset & questions

- Main questions:
  - Are there any outliers in the dataset?
  - What subgroups make up for the dataset?
  - What are the characteristics of particular subgroups?
  - What are the biological reasons that underlie such dataset structure?

515 samples

277 male ♂ 238 female ♀

44 attributes

Dataset & questions

- Main questions:
  - Are there any **outliers** in the dataset?
  - What **subgroups** make up for the dataset?
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  - What are the **biological reasons** that underlie such dataset structure?

515 samples

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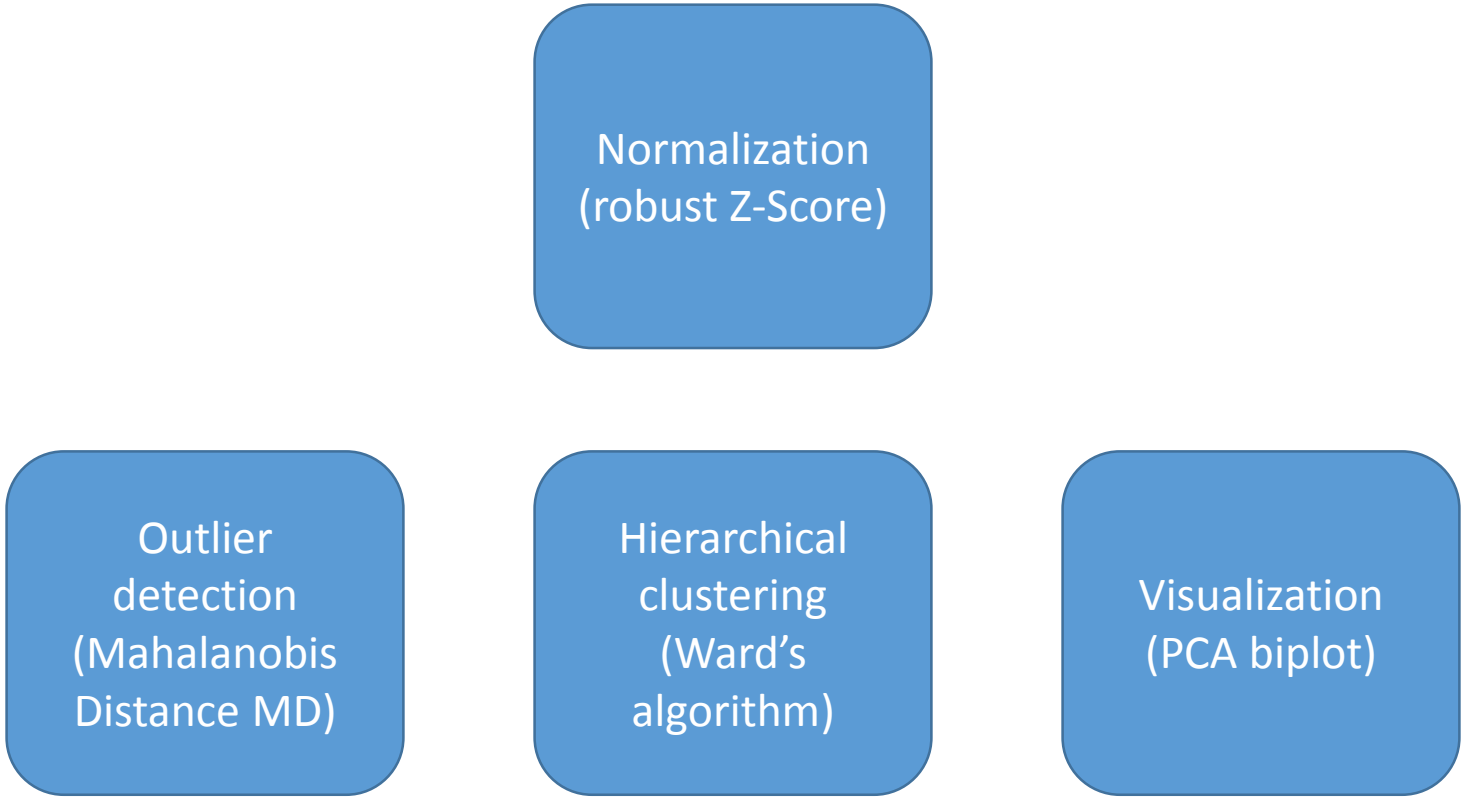
44 attributes

23 numerical	21 nominal
AGE, BMI, GLUCOSE, …	COUNTRY. REGION, YEAR.SEASON OBESITY,…

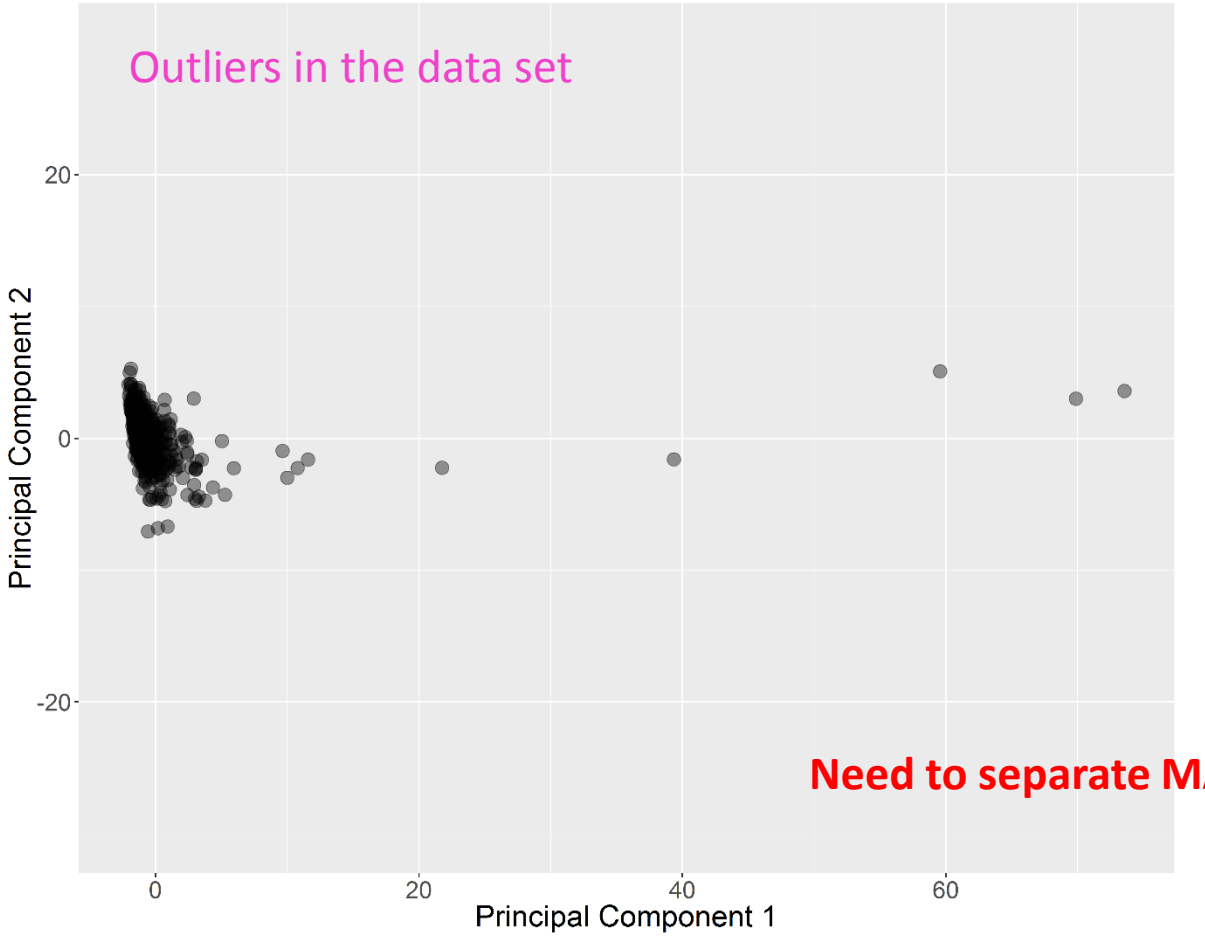
Overview of data processing procedure

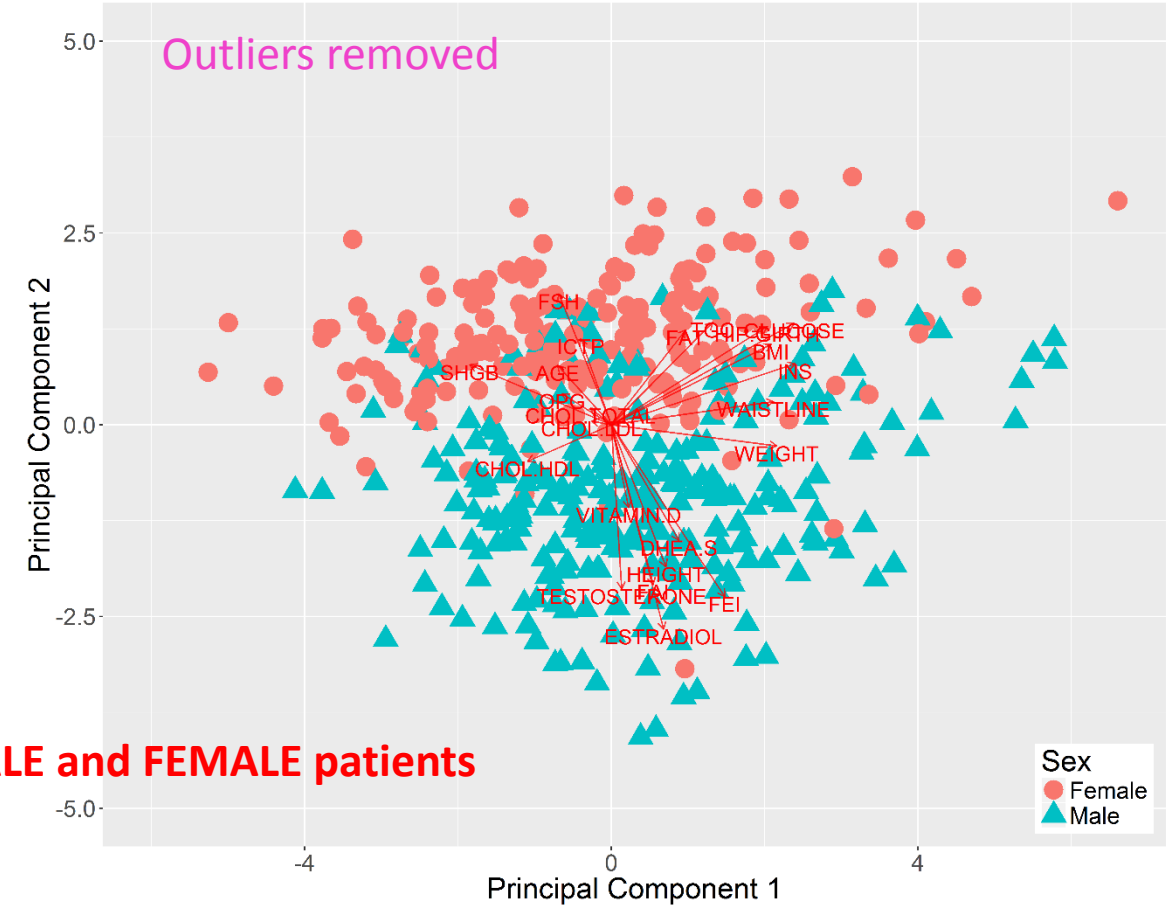


All based on data variance.

(Murtagh, Legendre, 2014)

Introductory analysis





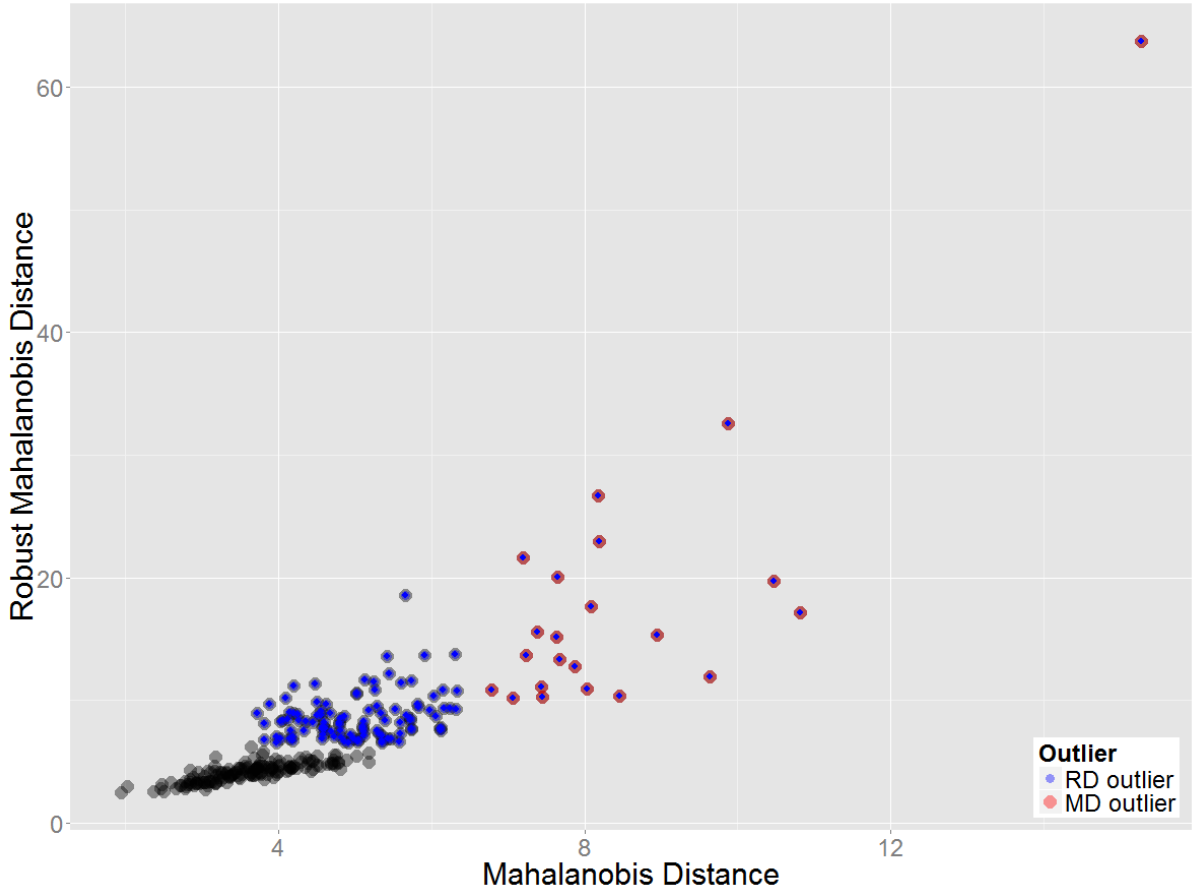
Need to separate MALE and FEMALE patients

Male set analysis - outlier removal

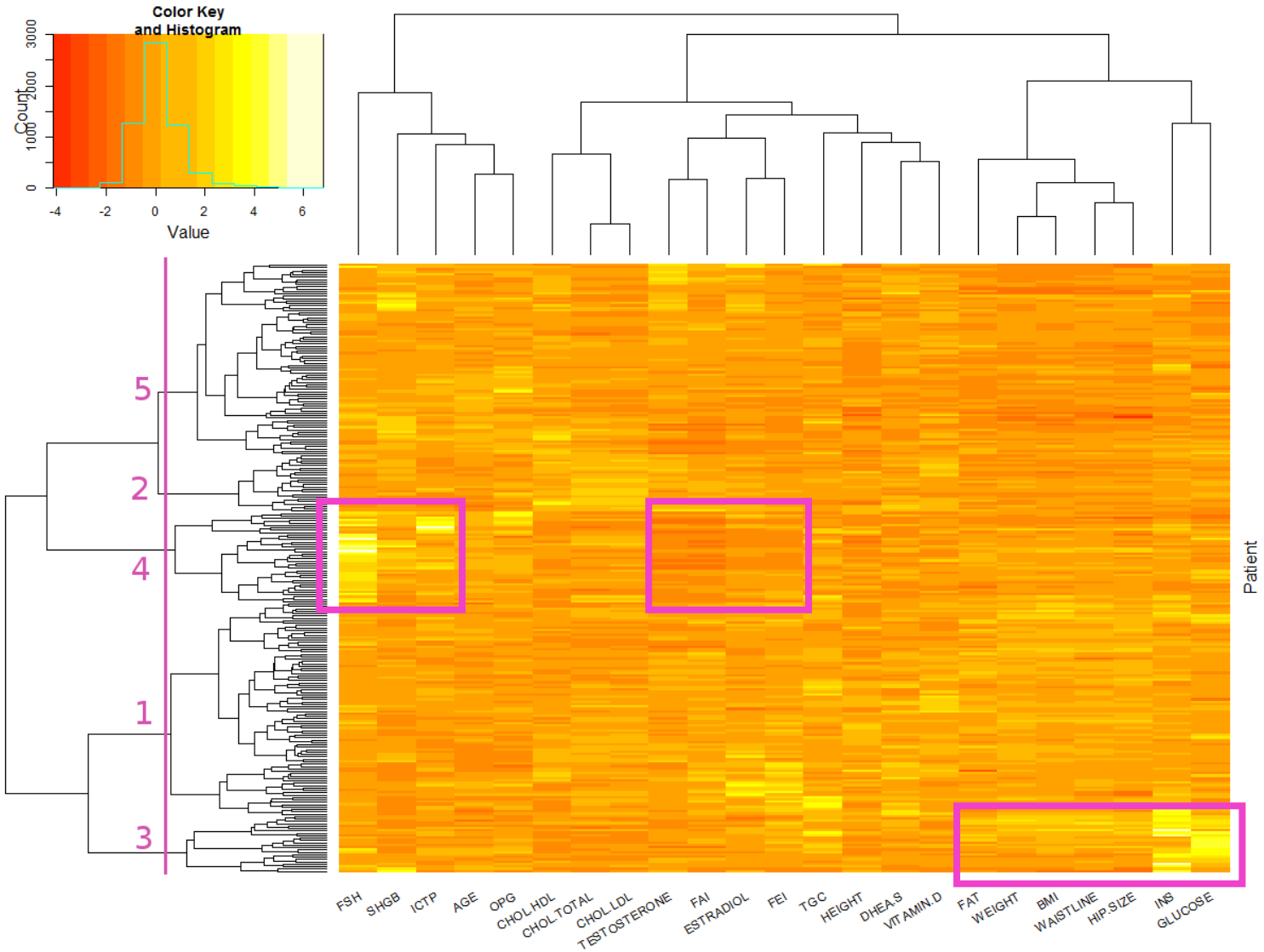
- Outliers based on **Mahalanobis Distance (MD)**:
  - **22 patients**

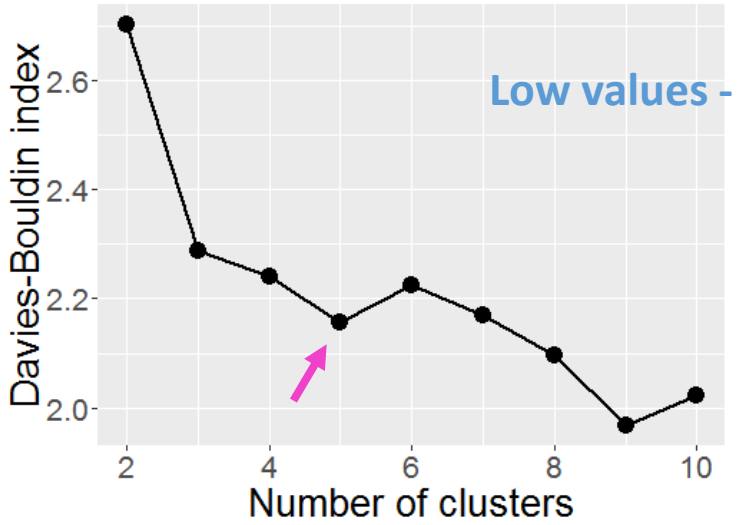
- Outlier detection with **robust Mahalanobis Distance (rMD)**:
  - **124 patients**

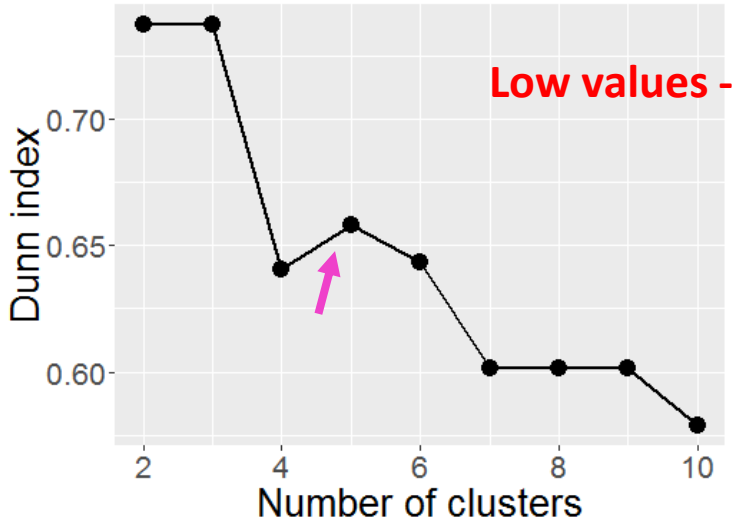
The data set is heterogeneous and may contain subgroups



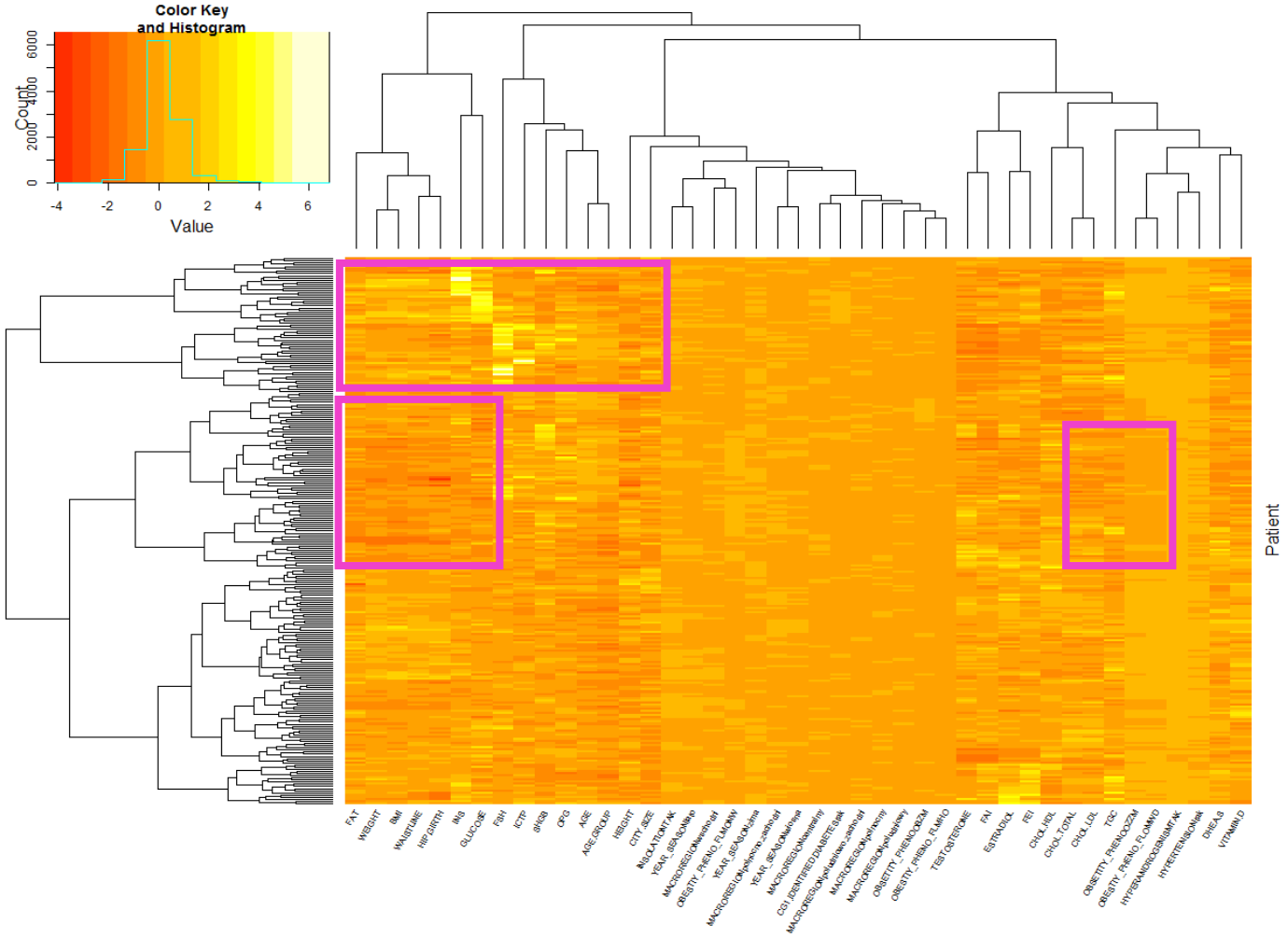
Male set analysis – hierarchical clustering



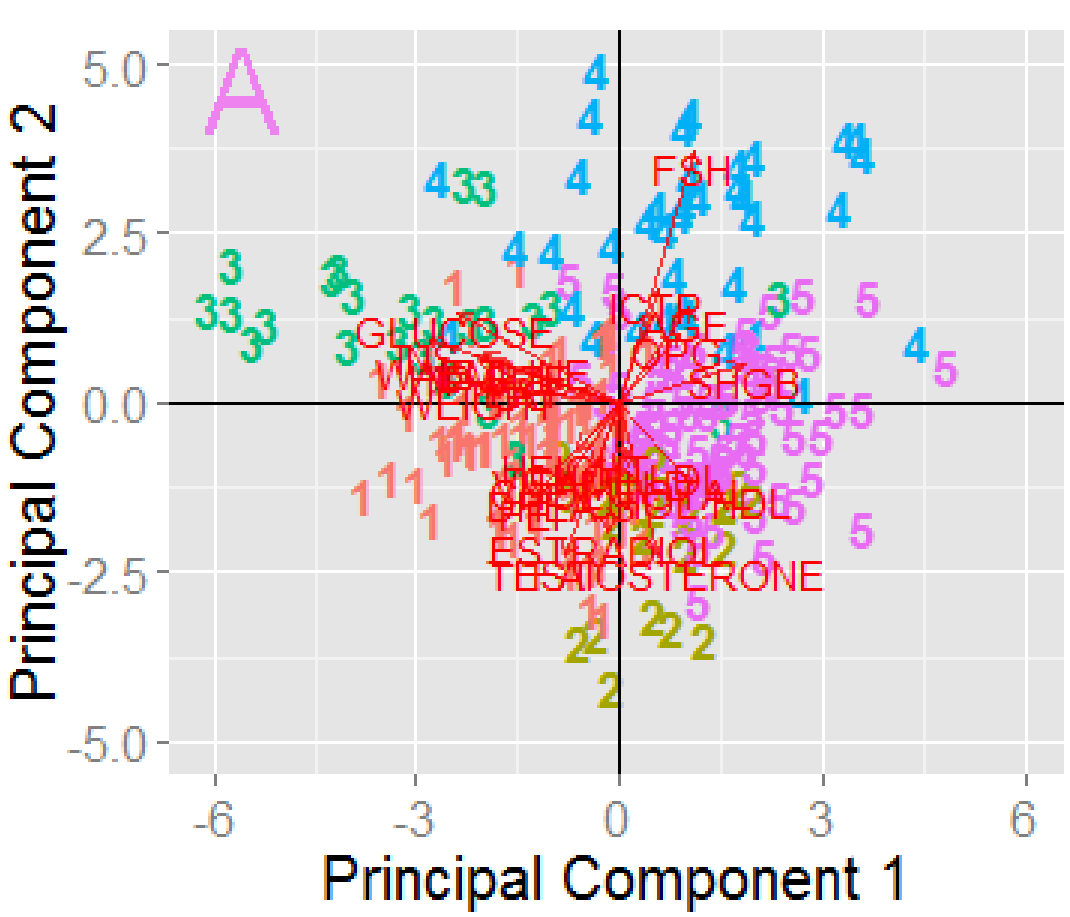


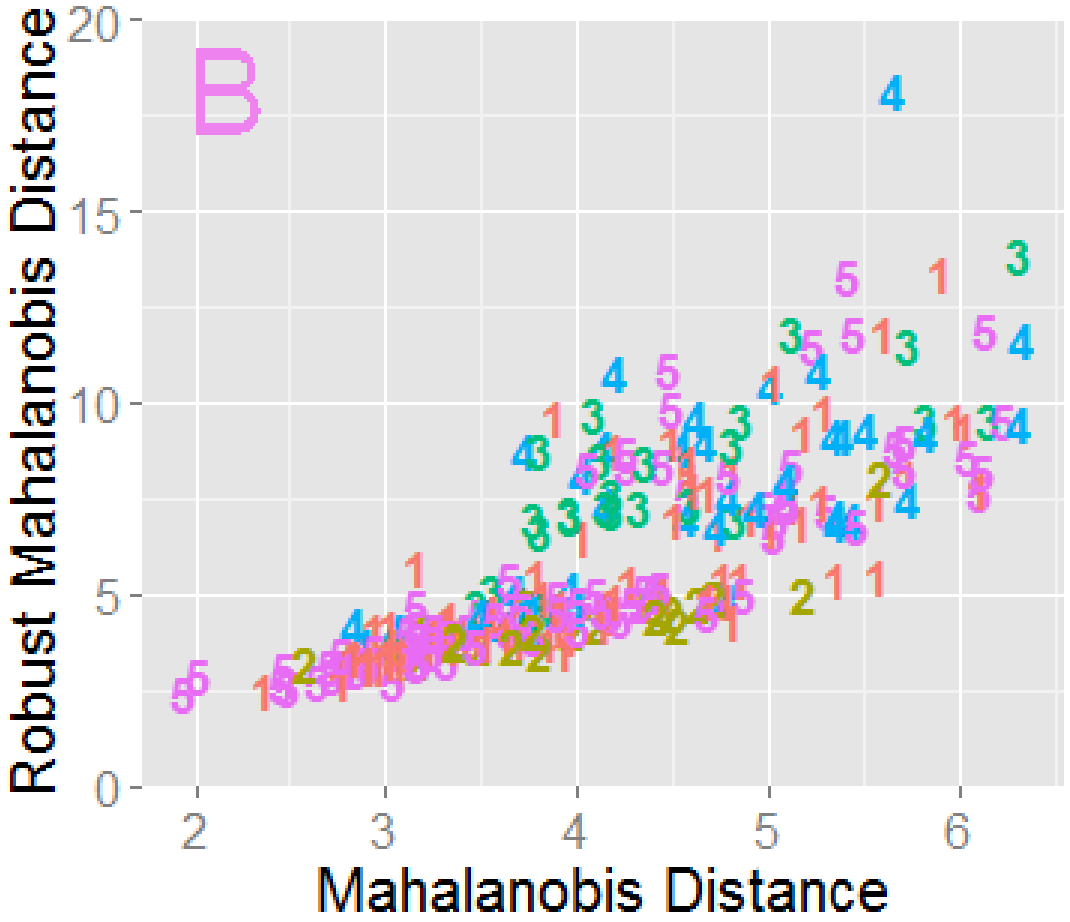


Addition of categorical data



Male set analysis – summarizing data





Methodological conclusions

- MD vs rMD plot
  - Emphasis of the data set heterogeneity
- Ward's hierarchical clustering + PCA
  - Consistent grouping & visualization of patient groups
- PCA with biplot vectors
  - Facilitated biological interpretation of structure of the data

Tutorial paper to be submitted to ***Statistics in Medicine (Wiley)***

Biological conclusions

- There are 5 distinct patient subgroups
  - **Among them patients with elevated FSH and low TESTOSTERONE (hypogonadism)**
- There are three groups of attributes:
  - Age-related attributes
  - Obesity-related attributes
  - Sex-hormones related and other

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Additional slides

Why use the Ward's algorithm

Outlier detection (Mahalanobis Distance MD)

Hierarchical clustering (Ward's algorithm)

Visualization (PCA)

$$MD(x_i) = \sqrt{(x_i - \bar{X})S^{-1}(x_i - \bar{X})},$$

where :

S $-$ *covariance matrix*

$$Var(I) = V(Q) + \sum_{q \in Q} \frac{m_q}{m_I} V(q)$$

Maximize inter-cluster variance

Minimize within cluster variance

$$V(Q) = \sum_{\bar{x}_q \in Q} \frac{m_q}{m_I} (\bar{x}_q - \bar{X})^2 \qquad V(q) = \frac{1}{N_q} \sum_{x_i \in q} (x_i - \bar{x}_q)^2$$

Q – partitioning

q - cluster

$$T = XW$$
$$X^T X = W \Lambda W^T$$

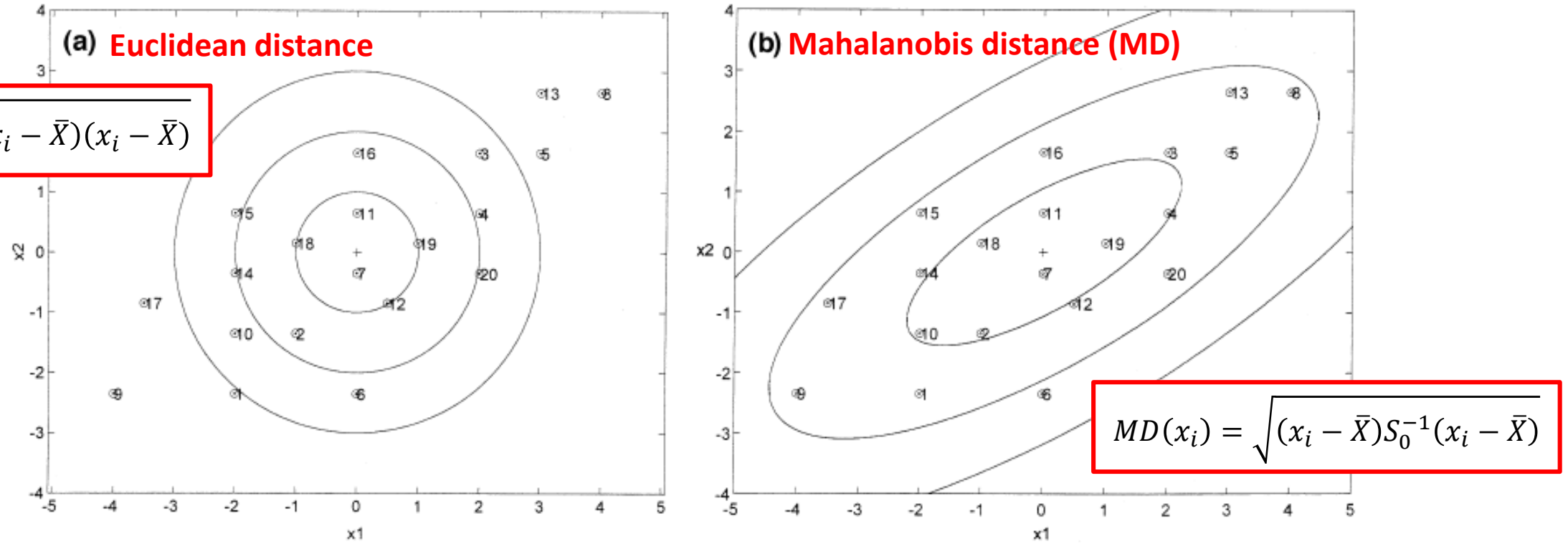
Λ – diagonal matrix of eigenvalues of $X^T X$ (S)

W – p-by-p matrix whose columns are eigenvectors of $X^T X$

Outlier detection with Mahalanobis Distance - intuition

De Maesschalck R, et al., Chemometrics and Intelligent Laboratory Systems 50 2000. 1–18

$$ED(x_i) = \sqrt{(x_i - \bar{X})(x_i - \bar{X})}$$



$$MD(x_i) = \sqrt{(x_i - \bar{X})S_0^{-1}(x_i - \bar{X})}$$

Fig. 1. (a) Plot of the simulated data for two variables x_1 and x_2 together with the circles representing equal EDs towards the center point. (b) Plot of the simulated data for two variables x_1 and x_2 together with the ellipses representing equal MDs towards the center point.

chemometrics: Multivariate Statistical Analysis in Chemometrics
http://cran.r-project.org/web/packages/chemometrics/index.html

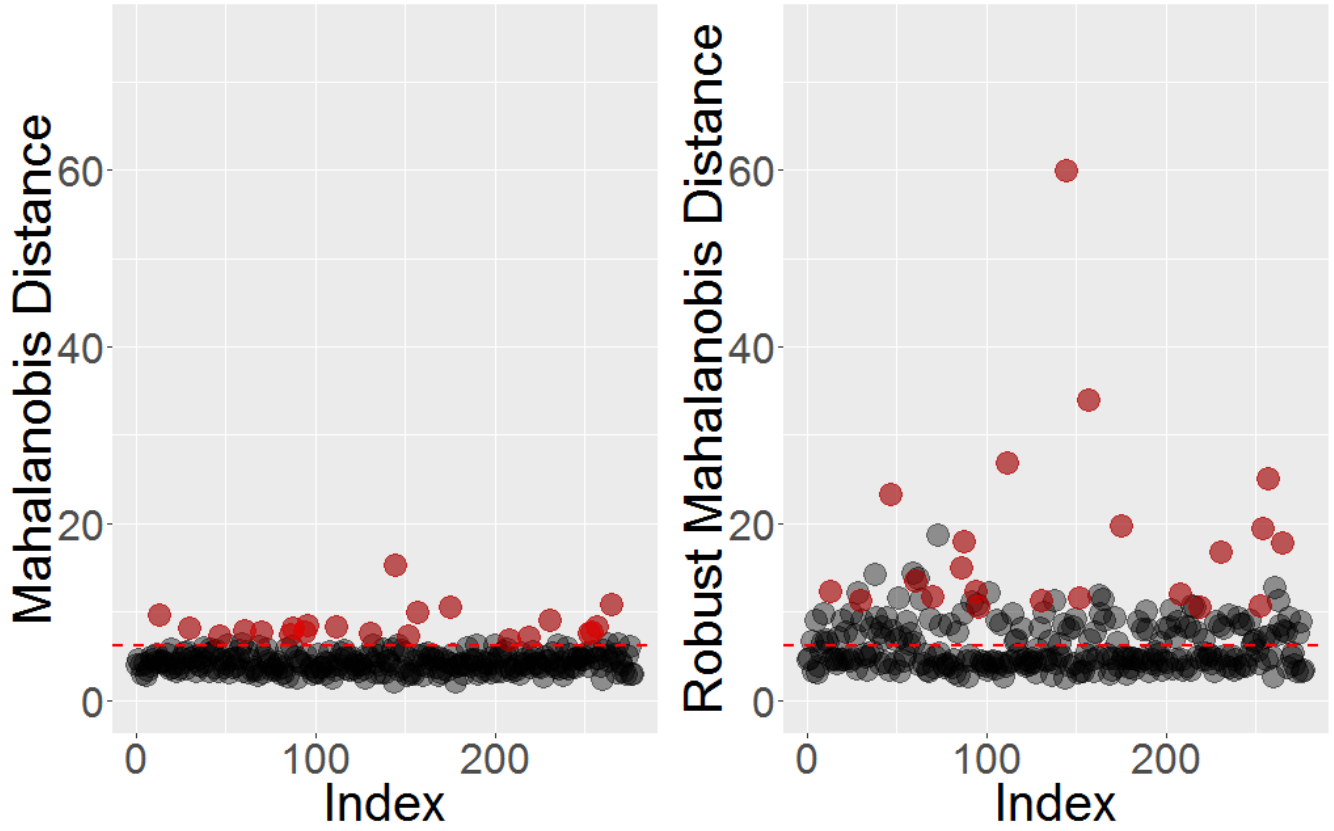
Male set analysis - outlier removal

- Outliers based on Mahalanobis Distance (MD):
  - **22 patients**

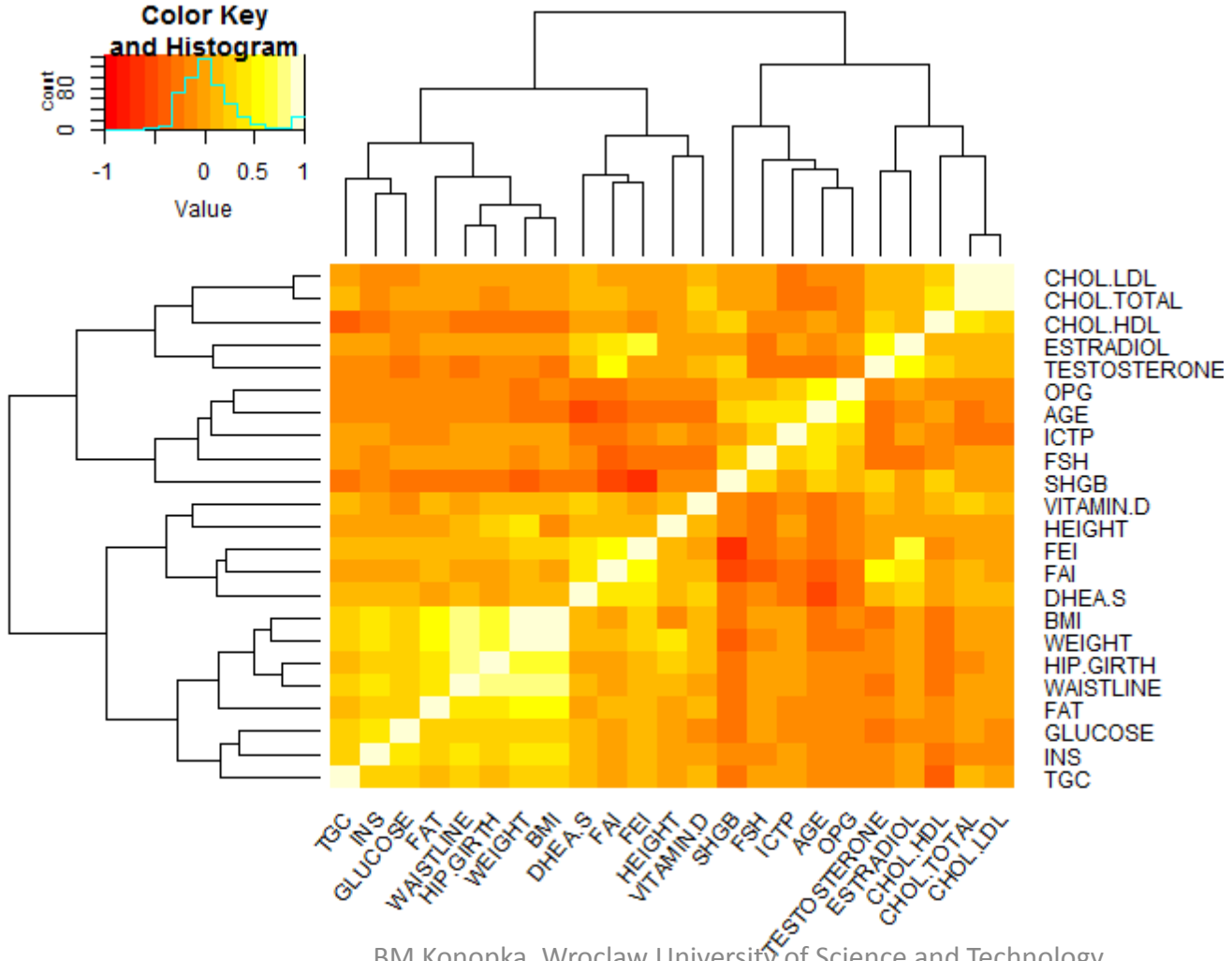
- Outlier detection with robust Mahalanobis Distance (rMD):

$$rMD(x_i) = \sqrt{(x_i - \overline{X_{\mathrm{k}}})S_{\mathrm{k}}^{-1}(x_i - \overline{X_{\mathrm{k}}})}$$

- Outliers based on robust MD:
  - **124 patients**

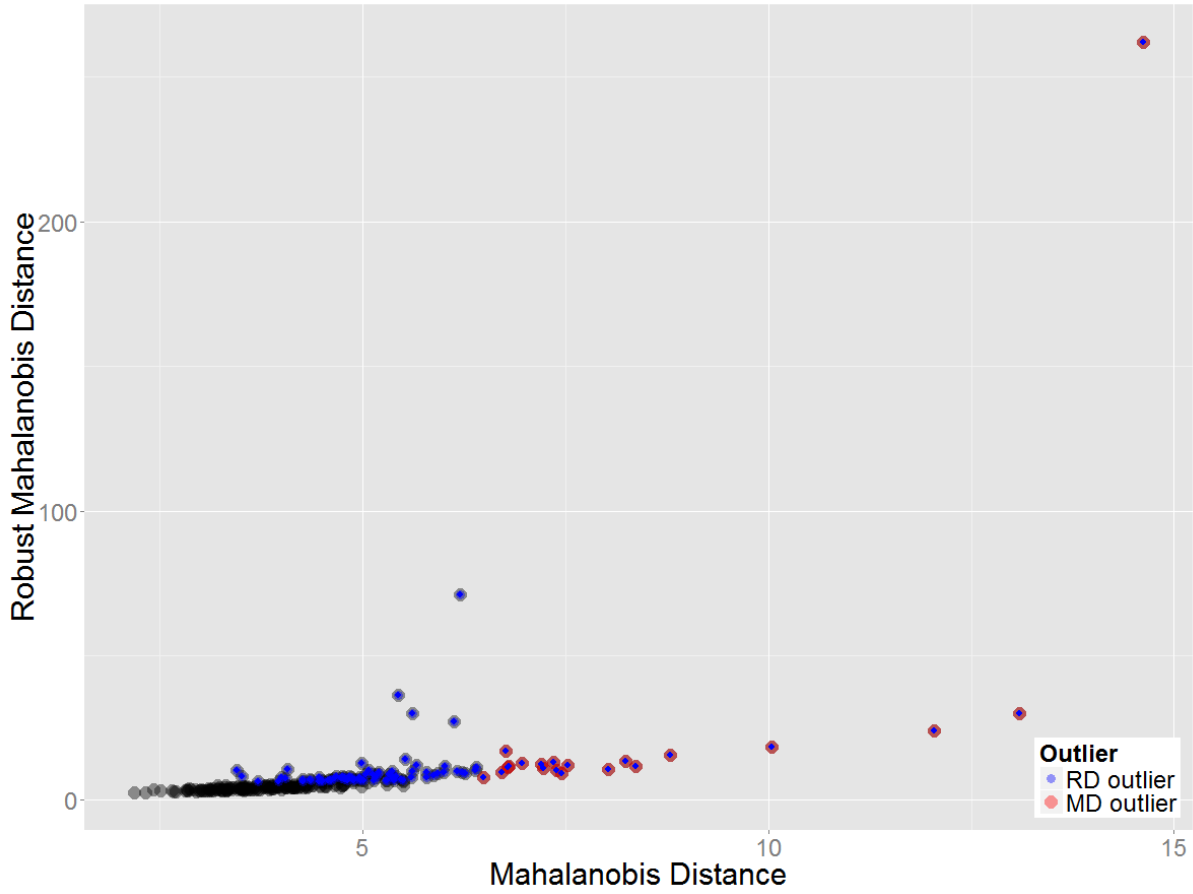


Clustering of attributes based on correlation

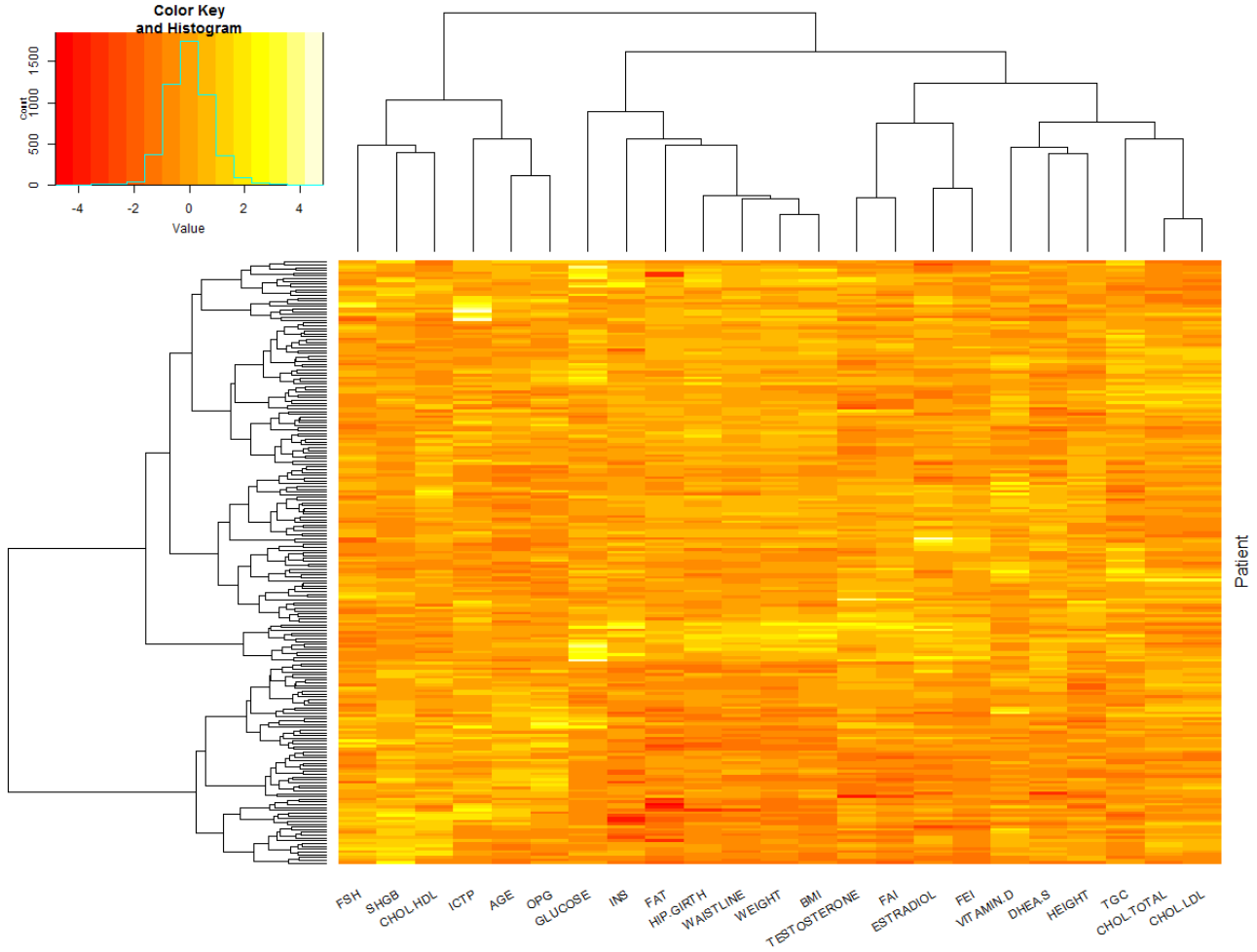


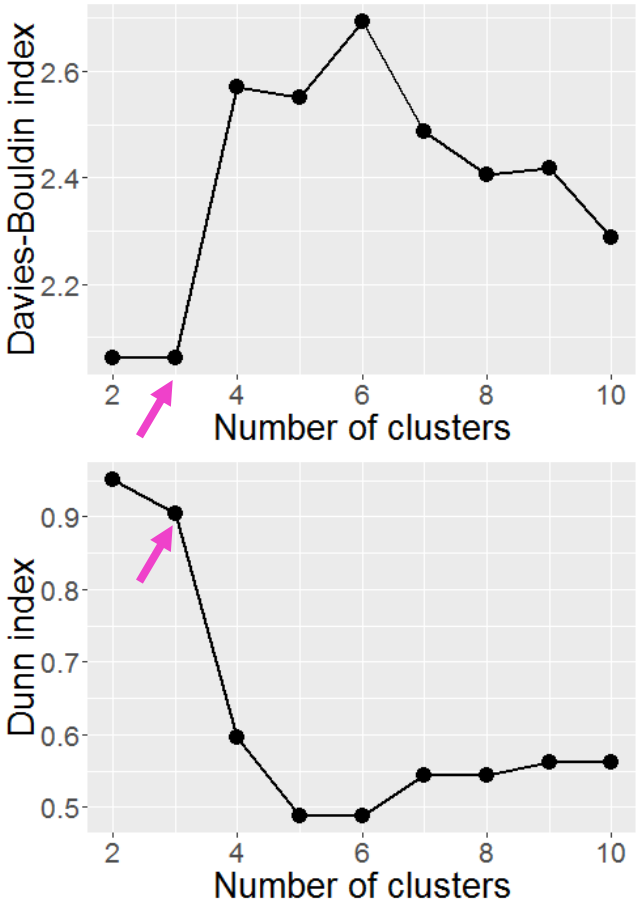
Female set analysis – outlier removal

- MD and rMD suggest removal of 20 and 70 data points
- Data points are more condensed



Female set analysis – hierarchical clustering





Female set analysis – hierarchical clustering

- Three subgroups have been identified
  - Cluster 3 – diabetes
- The set is more homogeneous
- Three groups of attributes have been identified:
  - Age-related attributes
  - Obesity-related attributes
  - Sex-hormones related and other