Insight

Clustering high dimensional mixed data: joint analysis of phenotypic and genotypic data

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- Motivating application: LIPGENE-SU.VI.MAX study. *'Diet, genomics and the metabolic syndrome: an integrated nutrition, agro-food, social and economic analysis.'*
- Aim: uncover any sub-phenotypes, identify discriminating variables, considering all data.

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- Diagnosed if have ≥ 3 abnormalities:

Fasting glucose concentration	$\geq$5.5 mmol l^{-1}
Serum TAG concentration	$\geq$ 1.5 mmol l^{-1}
Serum HDL-c concentration	$<$ 1.04 mmol l^{-1} (Men) $<$ 1.29 mmol l^{-1} (Women)
Blood pressure	Systolic BP $\geq$ 130 mm Hg Diastolic BP $\geq$ 85 mm Hg
Waist circumference	$>$ 94 cm (Men) $>$ 80 cm (Women)

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- Aim: model $J = A + B + C = 738$ variables simultaneously.

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  4. Is there a correspondence between the initial clusters and the 7-yr follow up diagnosis?

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- Early attempts employed latent variable models and location models:
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- Copula based approaches:
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  - Continuous data $\rightarrow$ factor analysis.

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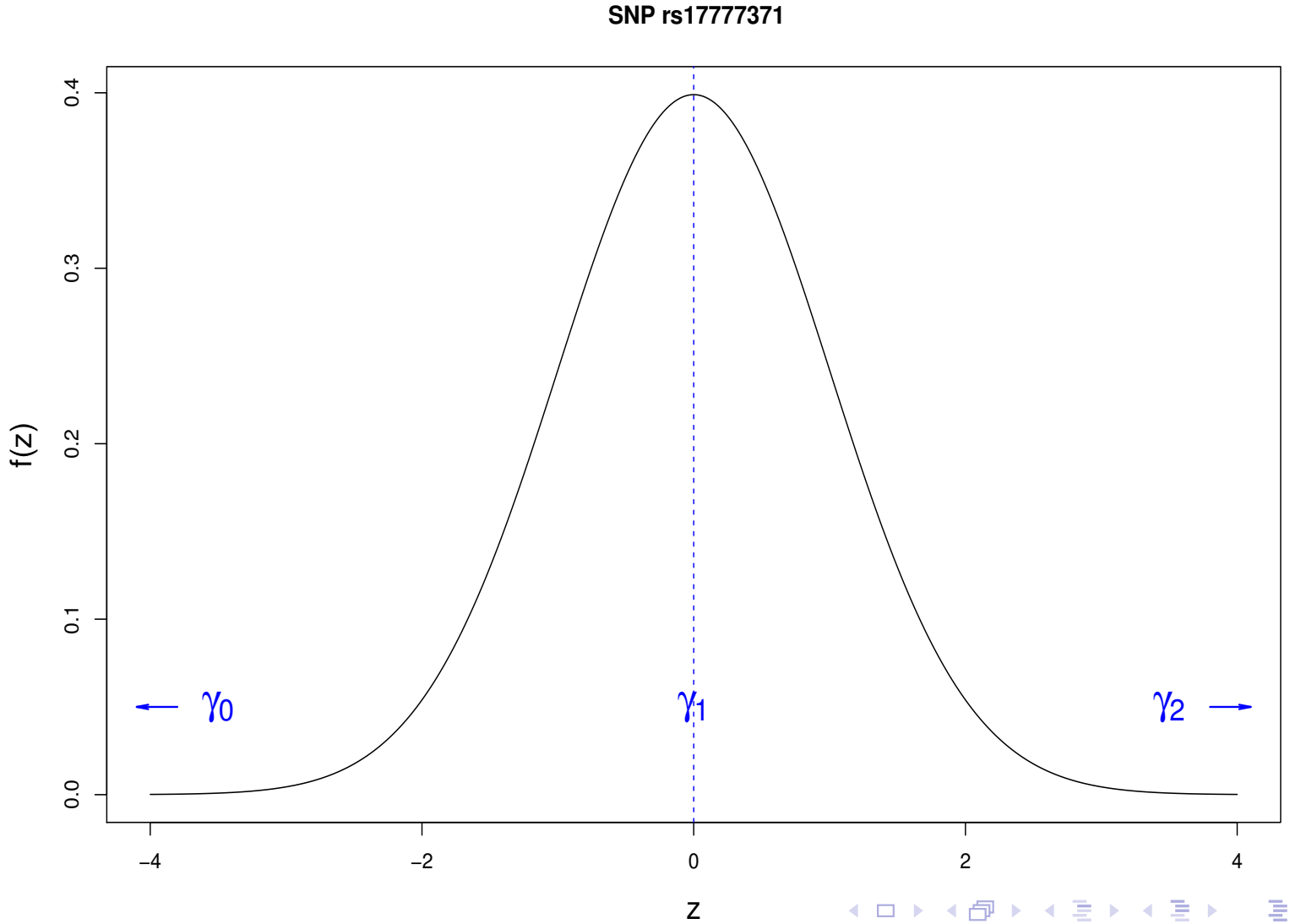

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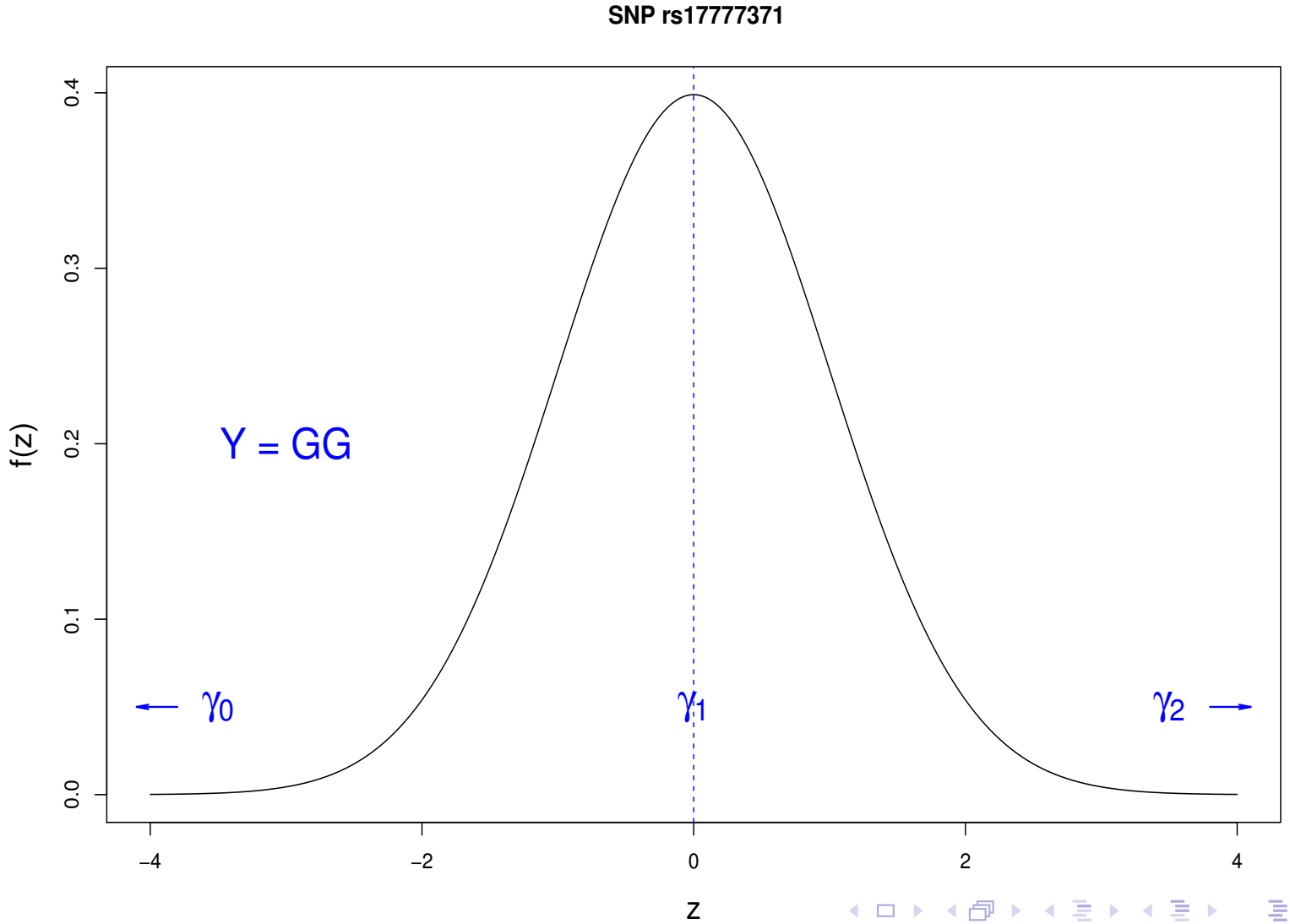

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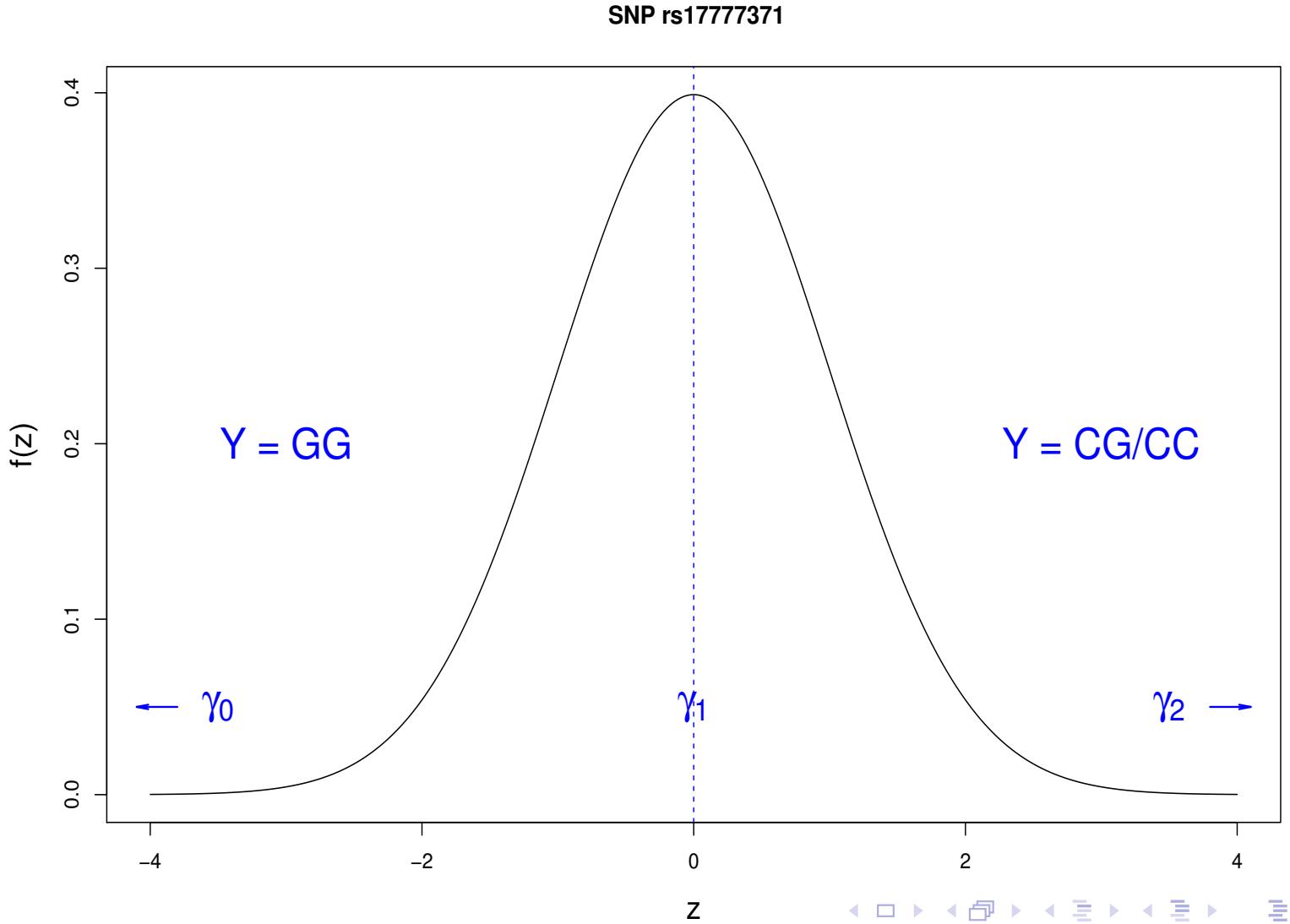

Item response theory model: factor analytic structure.

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$$\underline{z}_i = \underline{\mu} + \Lambda \underline{\theta}_i + \underline{\epsilon}_i$$

where

$\underline{\mu}$		C-vector of negative item difficulty parameters
Λ		$C \times Q$ matrix of item discrimination parameters
$\underline{\theta}_i$	$\sim$	$MVN_Q(\underline{0}, \mathbf{I})$
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- Dimension Q of the latent trait $\underline{\theta}_i$ is unknown, but $Q \ll C$.

$$\underline{z}_i | \underline{\theta}_i \sim \text{MVN}_C(\underline{\mu} + \Lambda \underline{\theta}_i, \mathbf{I})$$

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- Example: SNP `rs512535` $\in$ {AA, GG, AG}. Thus,

$$\underline{z}_{ij} = \{z_{ij}^1, z_{ij}^2\}$$

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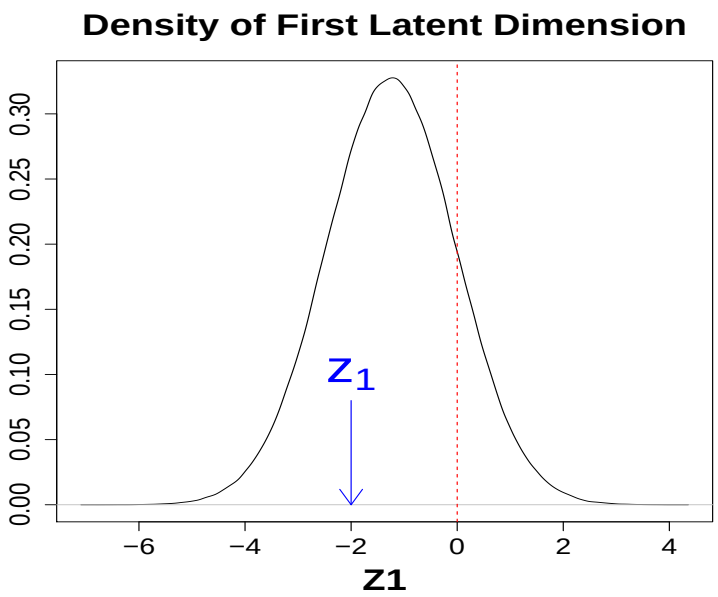
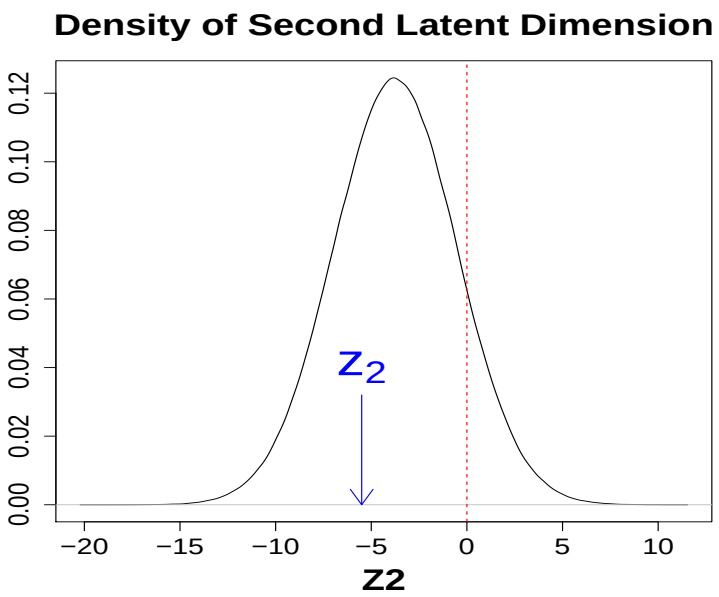
Damien:





$\Rightarrow$ AA

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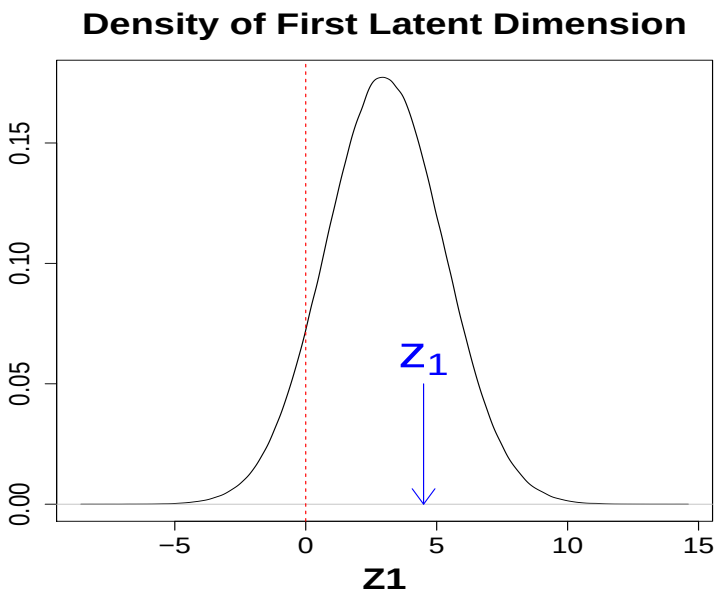
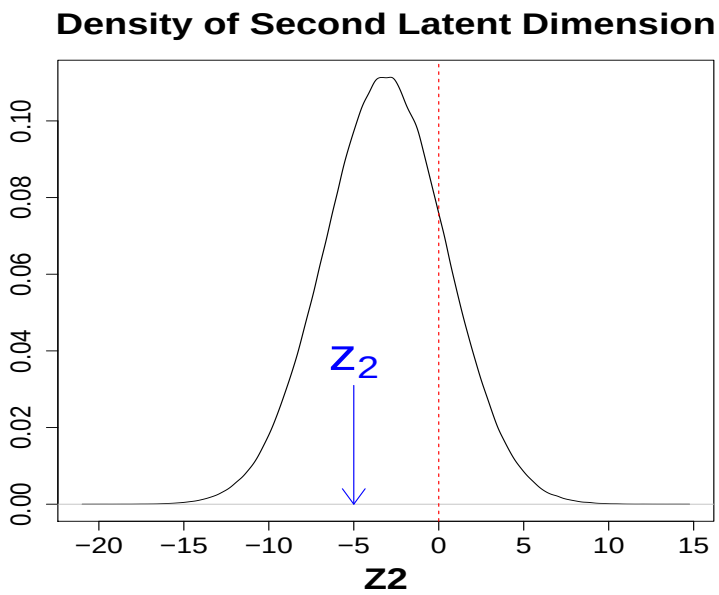
Lorraine:





$\Rightarrow$ GG

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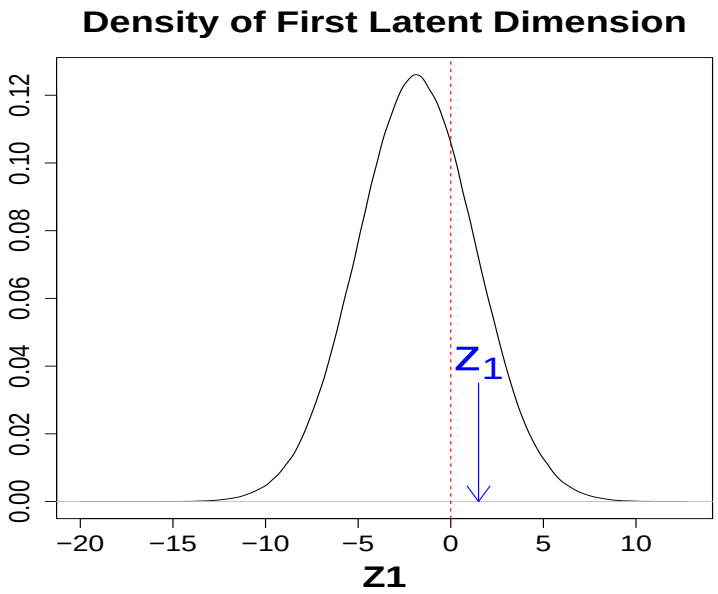
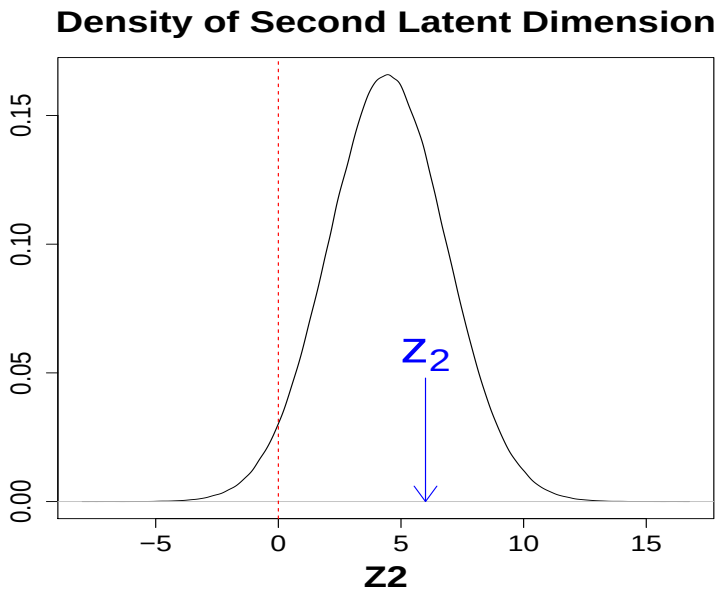
Claire:





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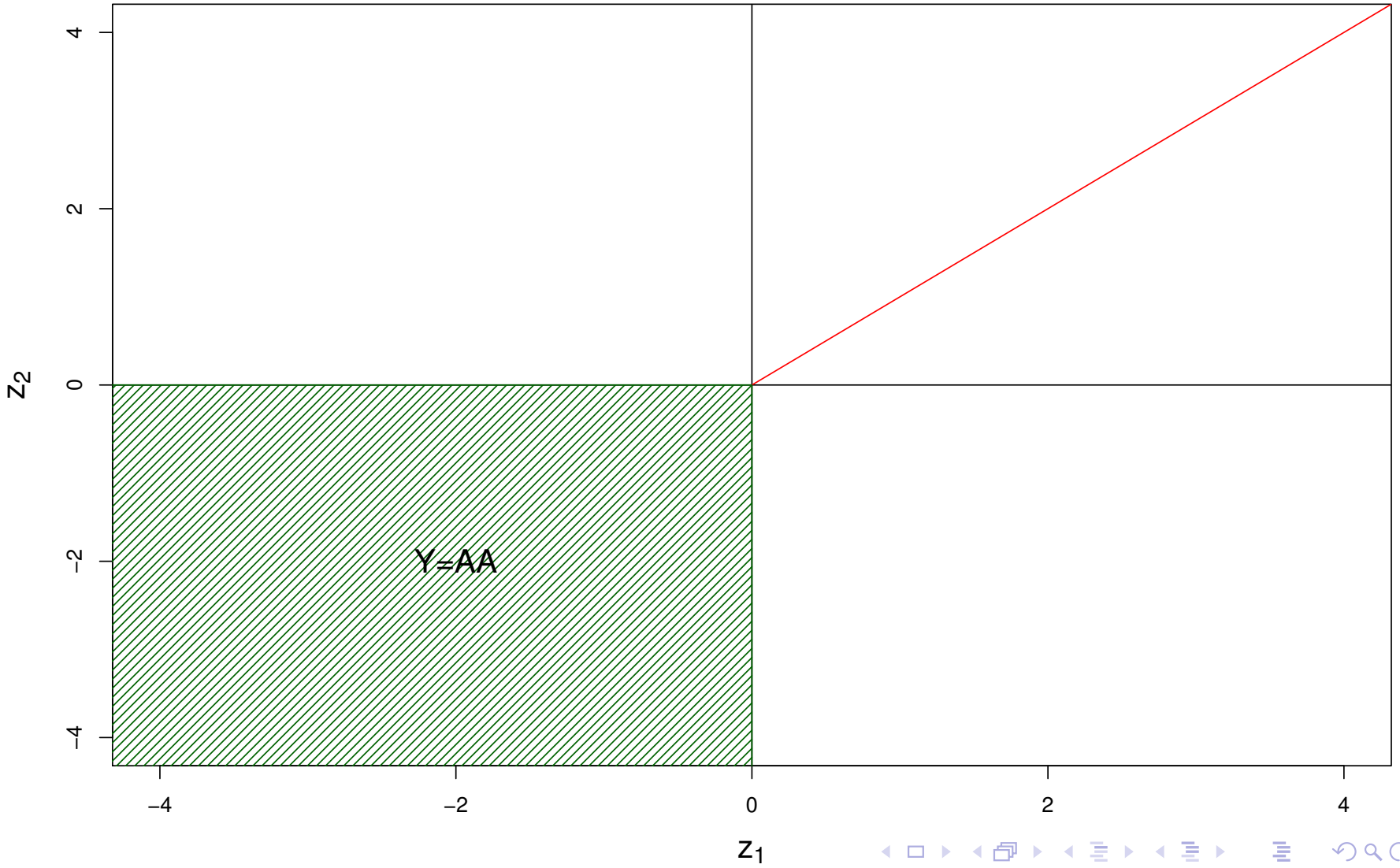
Another view...



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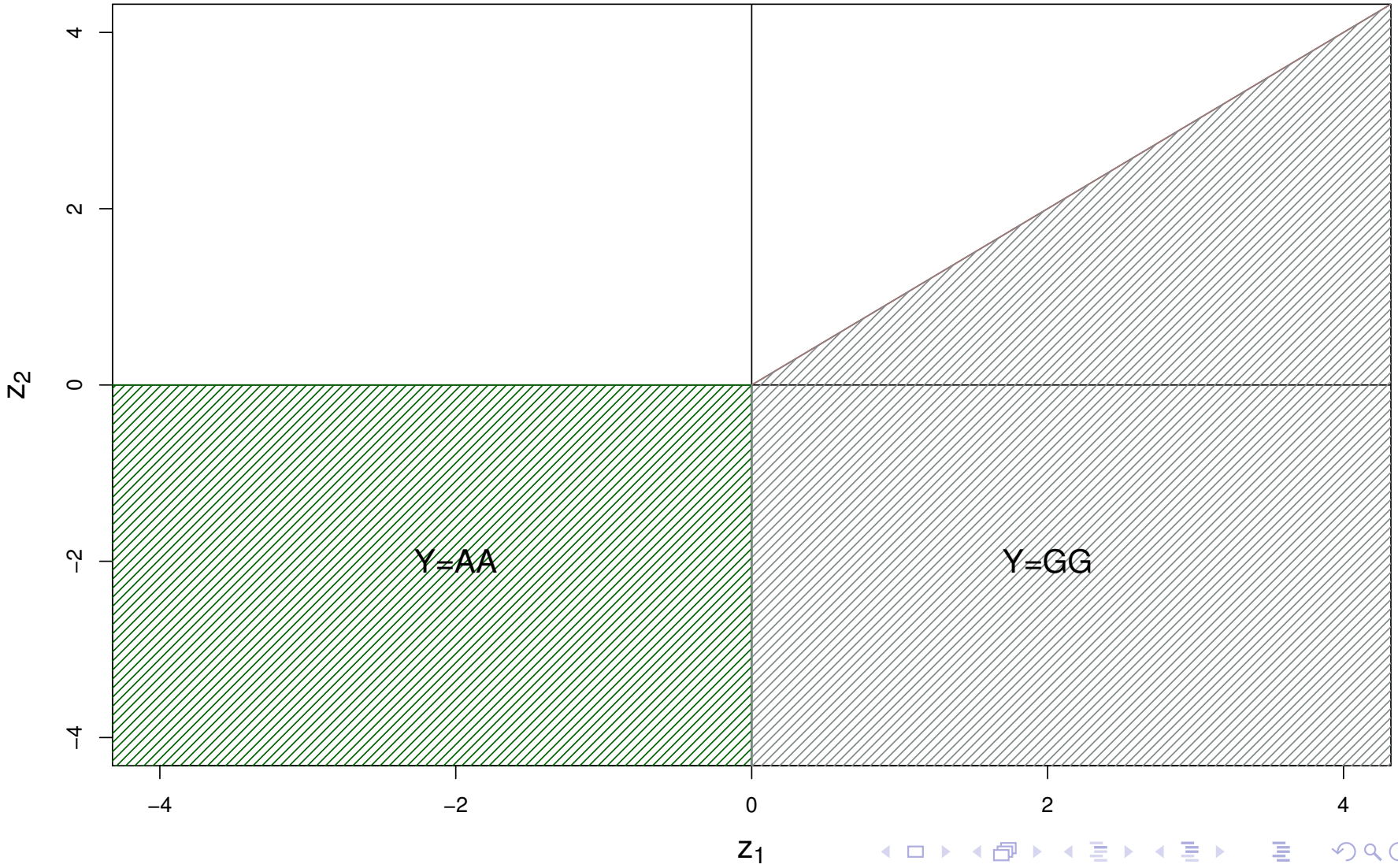

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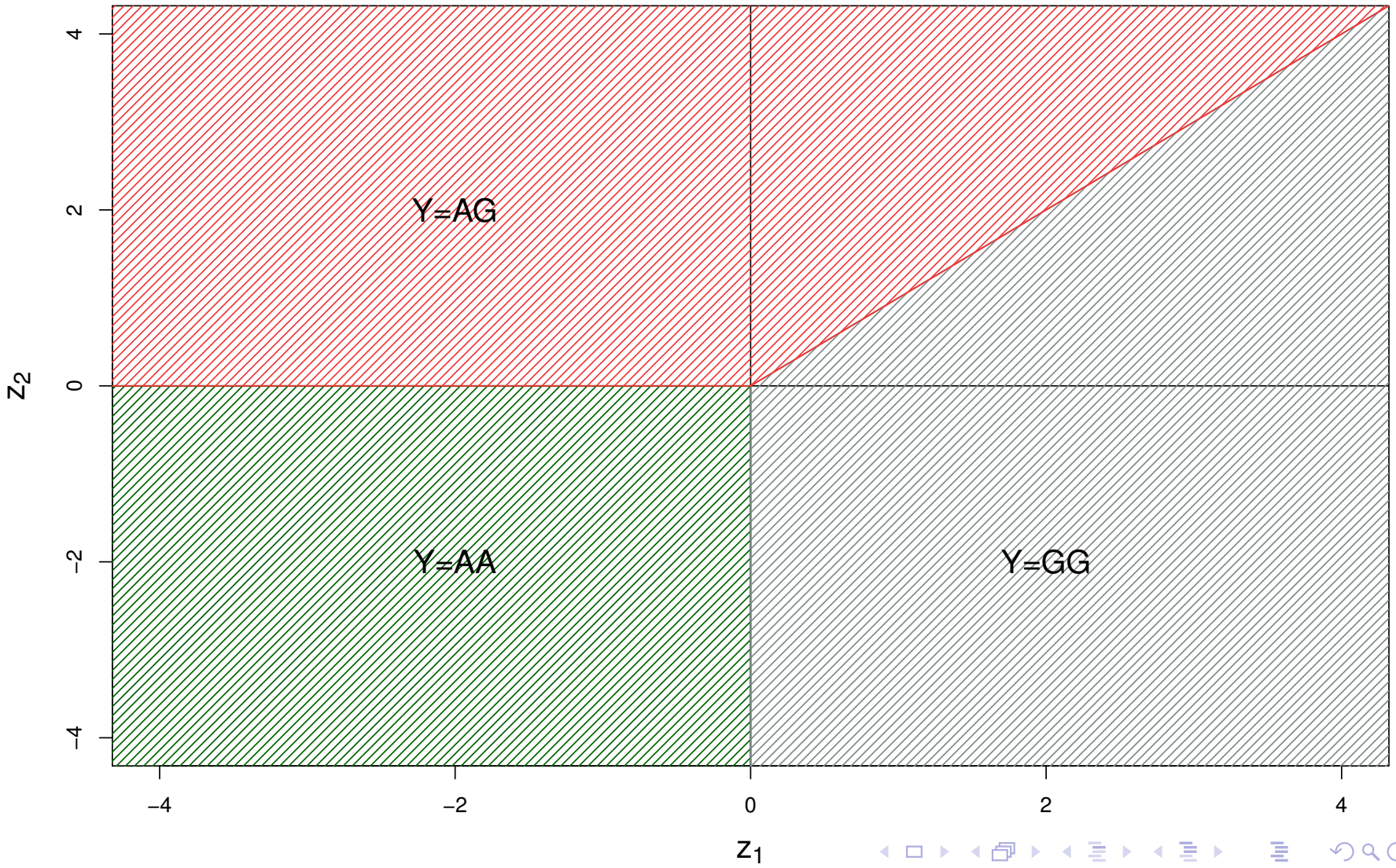

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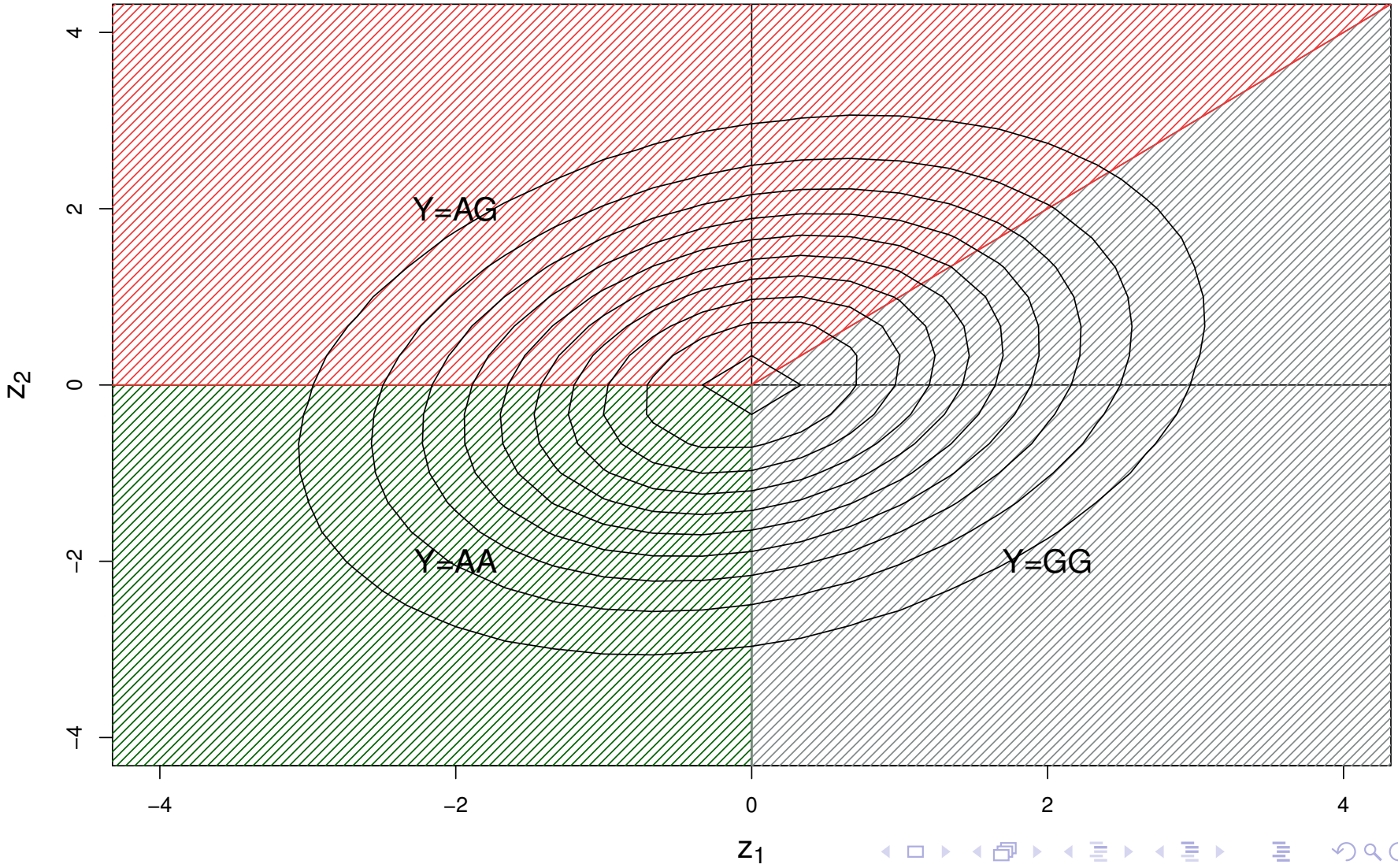

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- Marginally, have a parsimonious covariance structure:

$$\underline{z}_i \sim \text{MVN}_D(\underline{\mu}, \Lambda\Lambda^T + \Psi)$$

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- Complex, augmented, likelihood function:

$$\begin{aligned}\mathbb{P}(\underline{y}_i|\underline{\mu},\Lambda,\underline{z}_i,\Theta,\Gamma,\Psi) \quad = \quad & \prod_{j\ \text{cns}} N(\mu_j+\underline{\lambda}_j^T\underline{\theta}_i,\psi_j) \\ & \times \prod_{j\ \text{bin}} N^T(\mu_j+\underline{\lambda}_j^T\underline{\theta}_i,1)\mathbb{I}\{z_{ij}\} \\ & \times \prod_{j\ \text{nom}}\prod_{k=1}^{K_j-1} N^T(\mu_j^k+\underline{\lambda}_j^{kT}\underline{\theta}_i,1)\mathbb{I}\{z_{ij}^k\}\end{aligned}$$

Mixture of factor analysers for mixed data (MFA-MD)

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- Each of G clusters modelled using an FA-MD model.
- Clustering occurs at the latent variable level:

$$\mathbb{P}(\underline{z}_i) = \sum_{g=1}^{G} \pi_g \, \text{MVN}_D(\underline{\mu}_g, \Lambda_g \Lambda_g^T + \Psi)$$

- Means and loadings are cluster specific; for parsimony $\Psi_g = \Psi_{g'}$.

Variable selection, Bayesian inference and model selection.

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- Small values of VR_j indicate that variable j discriminates between clusters.
- If $VR_j > \tau$ then variable j is dropped from the model.

Bayesian inference.

- For each participant, employ latent indicator variable:

$$\underline{\ell}_i \sim \text{Multinomial}(1, \underline{\pi})$$

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- Conjugate priors leads to Gibbs sampling.

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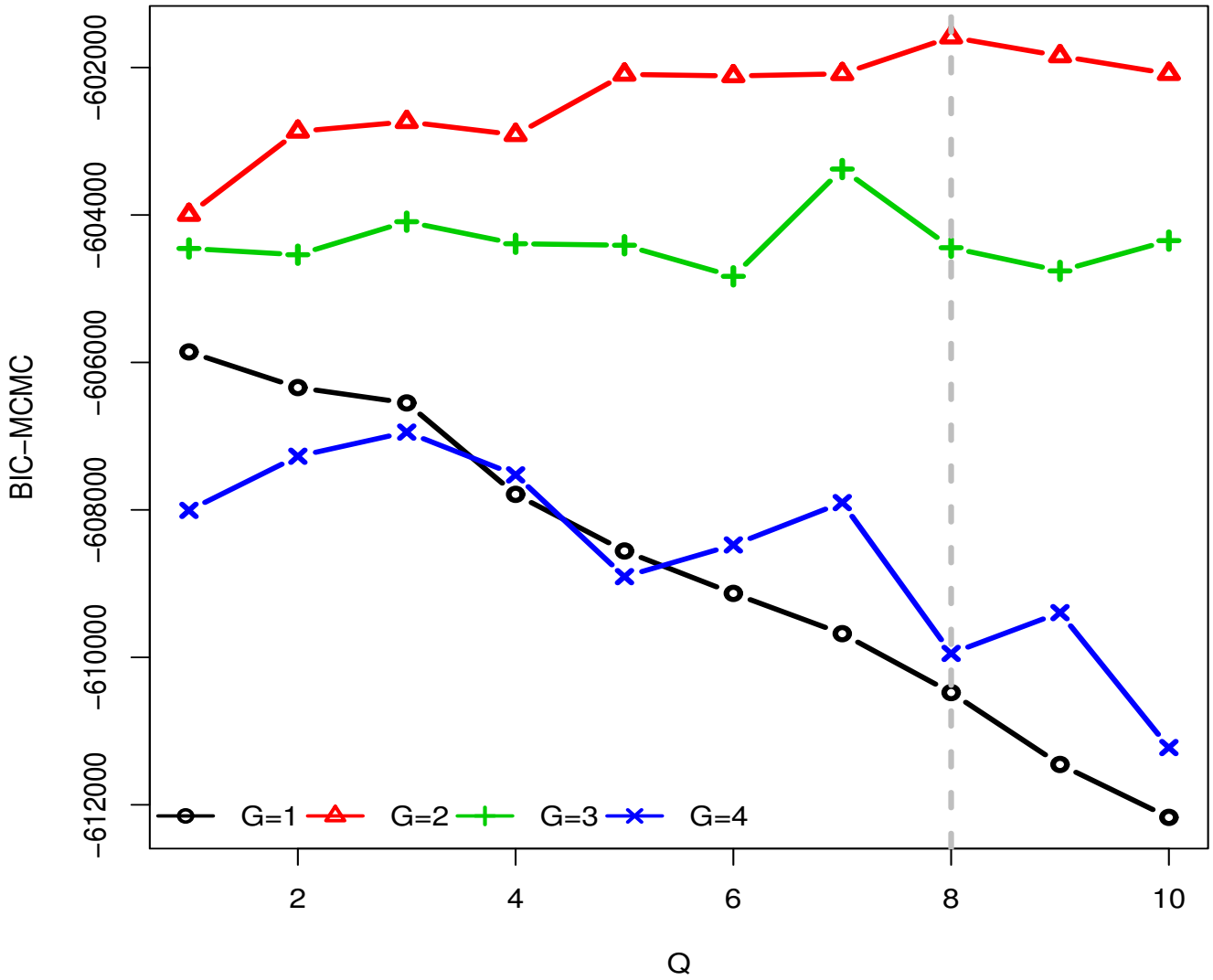
- For categorical variables, empirical probabilities are calculated from the observed data.
- Incorporate $\tilde{\mathcal{L}}$ in BIC-MCMC (Frühwirth-Schnatter (2011)):

$$\text{BIC-MCMC} = 2 \times \log \tilde{\mathcal{L}} - \nu \times \log(N)$$

Application to the LIPGENE-SU.VI.MAX cohort.

The optimal model: $G = 2$ and $Q = 8$.



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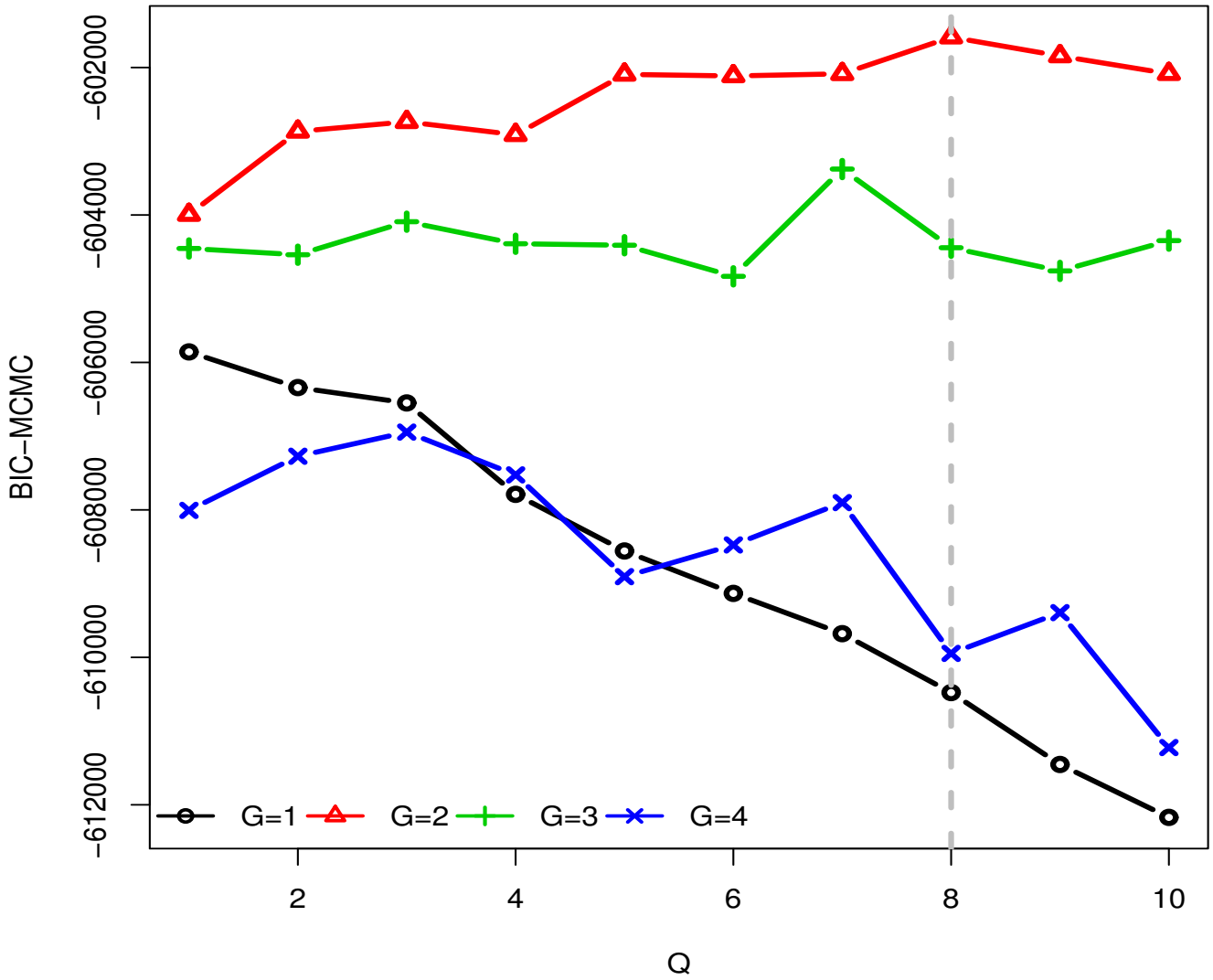
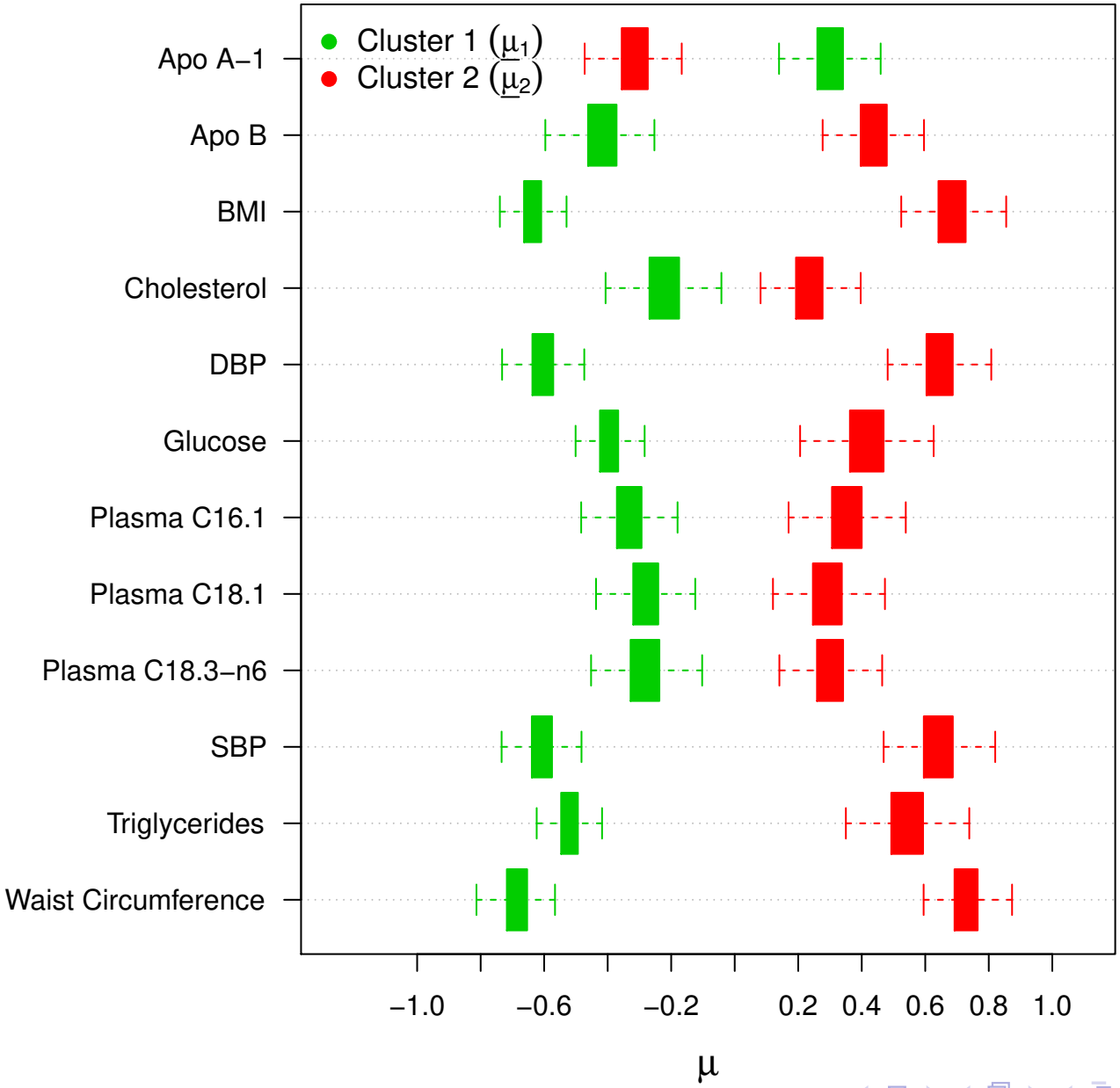
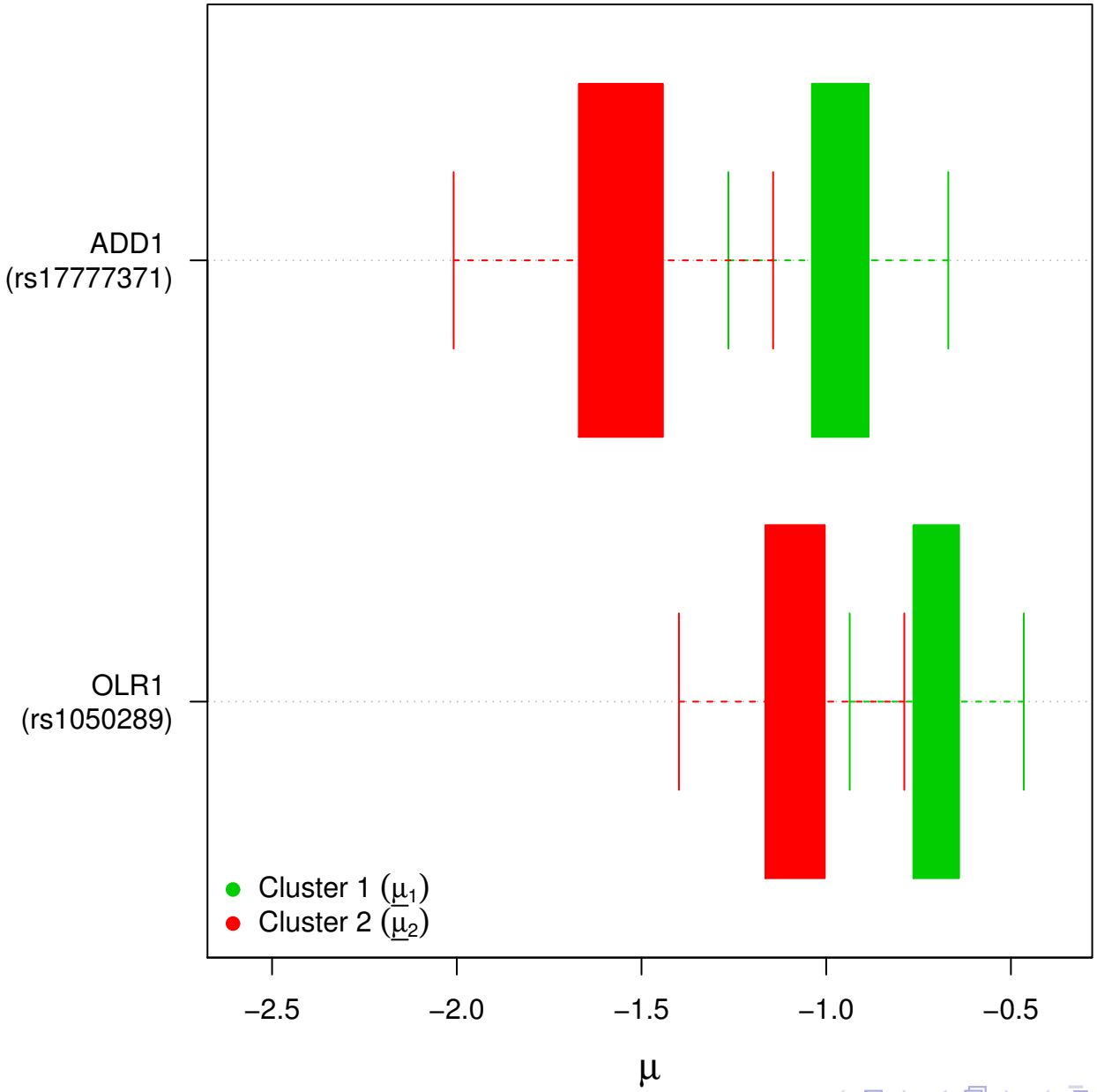


- Of the $J = 738$ original variables, 25 are retained: 12 phenotypic, 11 nominal SNPs and 2 binary SNPs.

Phenotypic cluster means



Binary SNP cluster means



SNP interpretations

Gene	SNP	Associated biological pathway
ADD1	`rs17777371`	Blood pressure regulation
APOB	`rs512535`	Lipid metabolism
APOL1	`rs136147`	Lipid metabolism
CETP	`rs4784744`	Lipid metabolism
GYS1	`rs2270938`	Glucose homeostasis
SLC6A14	`rs2071877`	Amino acid transporter
⋮	⋮	⋮

Correspondence between sub-phenotypes and 7-year follow-up diagnosis

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Initial data	Cluster 1 (‘Healthy’)	220	42
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Initial data	Healthy	194	31
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- Rand index: 0.69 (adjusted Rand: 0.38).
- Highlights the importance of utilising *both* phenotypic and genotypic factors.
- Suggests potential utility of early screening.

Quantifying sub-phenotype membership uncertainty

- Synonymous with concepts of precision medicine & nutrition.

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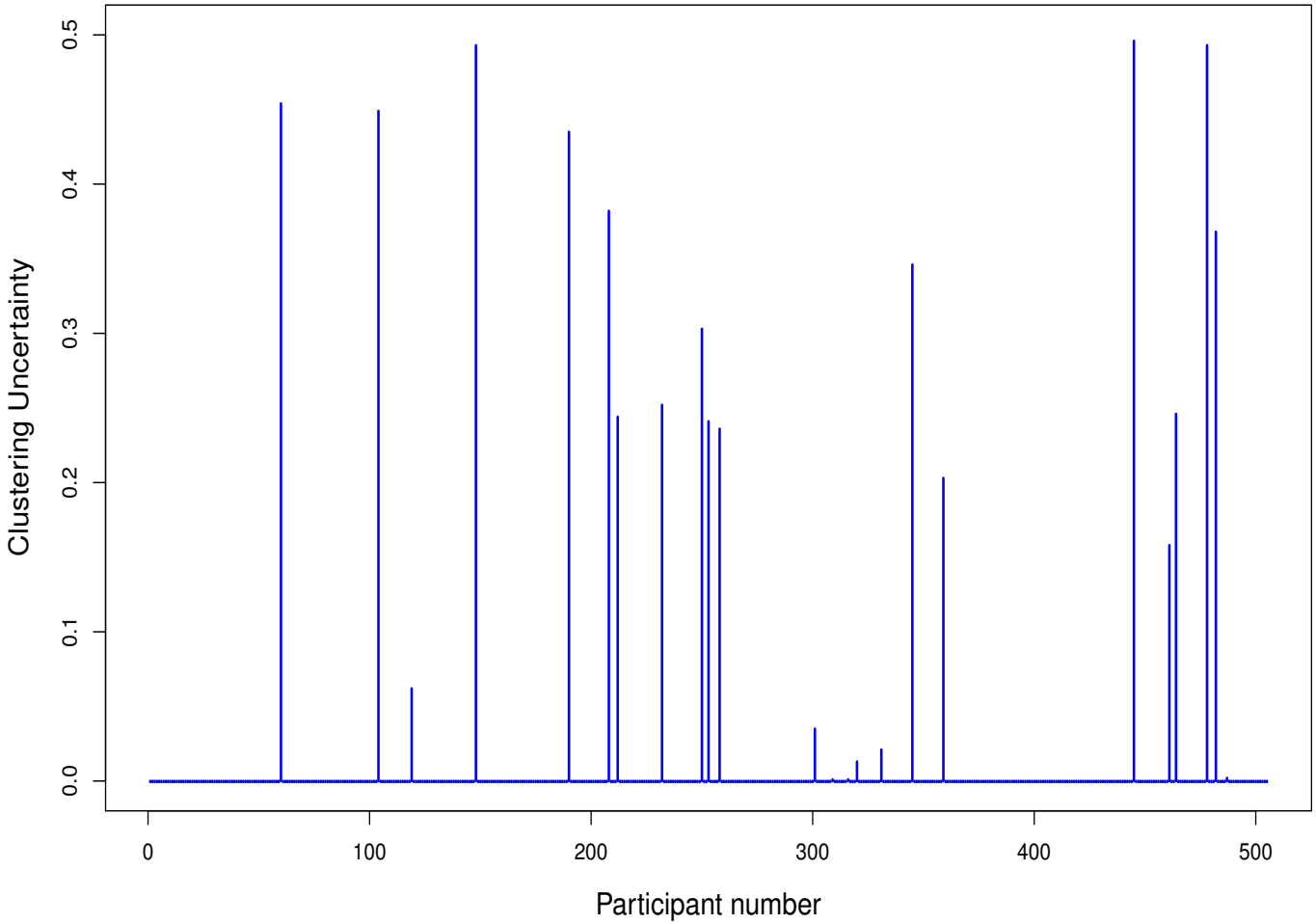

Assessing model fit

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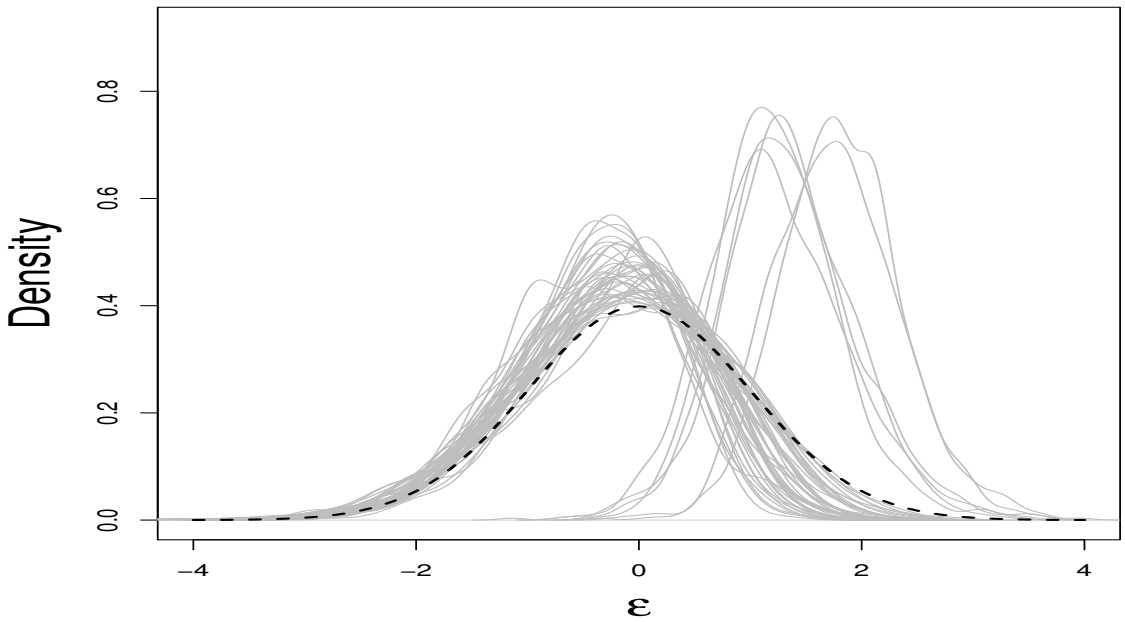
- Eg. Density estimates of the Bayesian latent residuals for the `rs17777371` SNP for 50 randomly selected participants.



Discussion and further work

- MFA-MD provides a method to cluster high dimensional data of mixed type in their innate form.
- Proposed approach can incorporate variable and model selection.
- Proposed method has applicability in any similar setting.

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- Proposed approach can incorporate variable and model selection.
- Proposed method has applicability in any similar setting.
- Highlighted influence of phenotypic and genotypic factors in the MetS.
- Highlighted the importance of early screening.
- Provides a tool to enable precision medicine.

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- Include other variable types e.g. count
- More model flexibility eg $Q_g \neq Q_{g'}$.
- Adapt to model longitudinal data.
- Variational approach to estimation should improve efficiency.

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- More model flexibility eg $Q_g \neq Q_{g'}$.
- Adapt to model longitudinal data.
- Variational approach to estimation should improve efficiency.
- Incorporate covariates such as gender etc.
- Improved approach to dealing with missing data in the LIPGENE-SU.VI.MAX cohort.

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