Obtaining a candidate set of covariates for genetic risk scores under data protection constraints in consortia

Daniela Zöller[1] Harald Binder[1]
Marcel Schniedermann[2] Dennis Kadioglu[1]

[1]Institute of Medical Biostatistics, Epidemiology and Informatics,
[2]Johannes Gutenberg University Mainz

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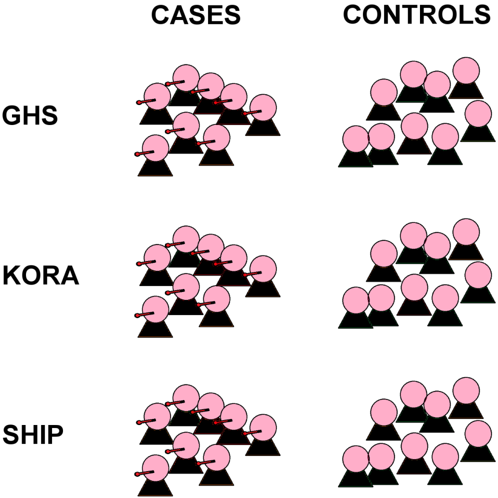
Genome-wide association study with focus on SNPs

Are there SNPs associated with disease status?

Can we obtain a genetic risk score?

$$E[y] = \mathbf{X}\underline{\beta}$$

Genome-wide association study with focus on SNPs



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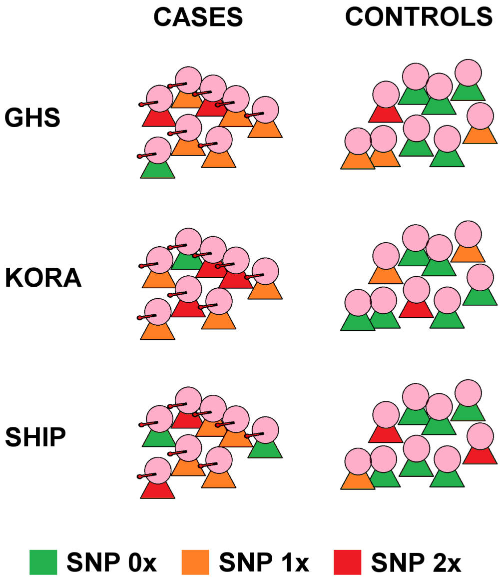

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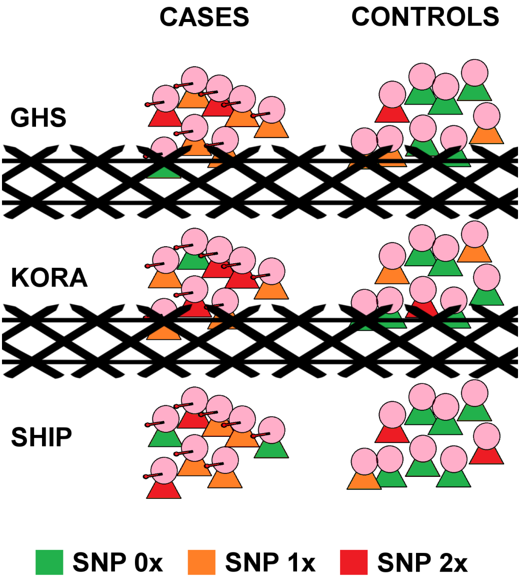

Goal: Multivariable genetic risk score

- Pool data from different cohorts
- Problem: Data protection constraints
  - Individual data not available for analysis
  - Aggregated data available
- Problem: High number of potential (correlated) SNPs

Our proposal: Distributed Boosting

Multivariable regularized stagewise regression model
incorporating automatic variable selection
using univariable effect estimates
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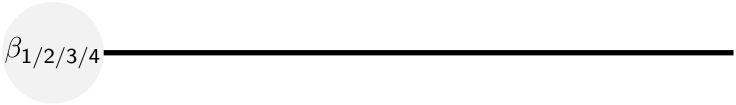
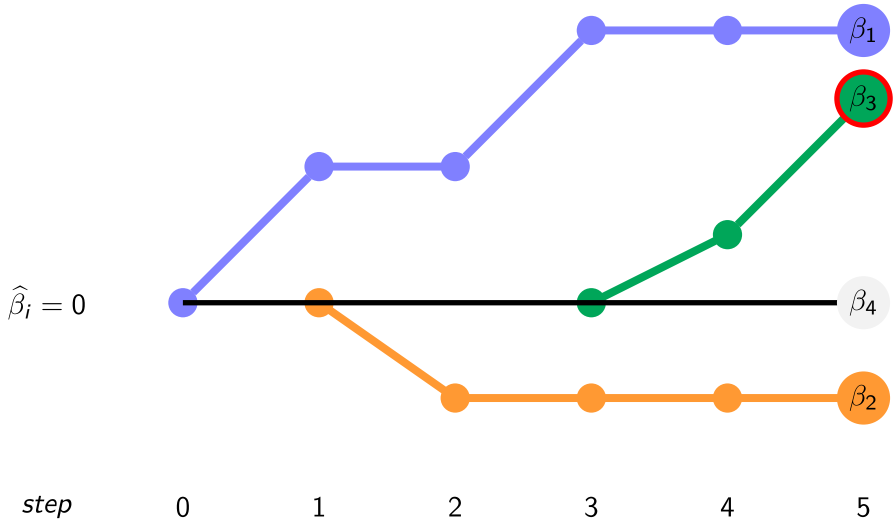
Boosting

$\widehat{\beta}_i = 0$



step 0 1 2 3 4 5

Boosting



Needed data for update in step (m+1) in a linear regression model

Score function for covariate j:

$$\widetilde{S}_j^{(m+1)} = x_j' r_{(j)}^{(m)}$$

$$= \sum_{i=1}^{n} x_{ij} \left(y_i - \widehat{y}_i^{(m)} \right)$$

$$= \sum_{i=1}^{n} x_{ij} y_i - \sum_{k:|\widehat{\beta}_k^{(m)}|>0} \widehat{\beta}_k^{(m)} \sum_{i=1}^{n} x_{ij} x_{ik}$$

$$\underset{\text{Univariable estimate}}{\uparrow} \qquad \underset{\text{Covariance of covariates}}{\uparrow}$$

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Assumptions

- Multivariate linear regression model
  - Response and covariates standardized
- Available data
  - Univariable estimates obtained from linear regression models
  - Covariance of already selected covariates with all covariates
- Several data providers
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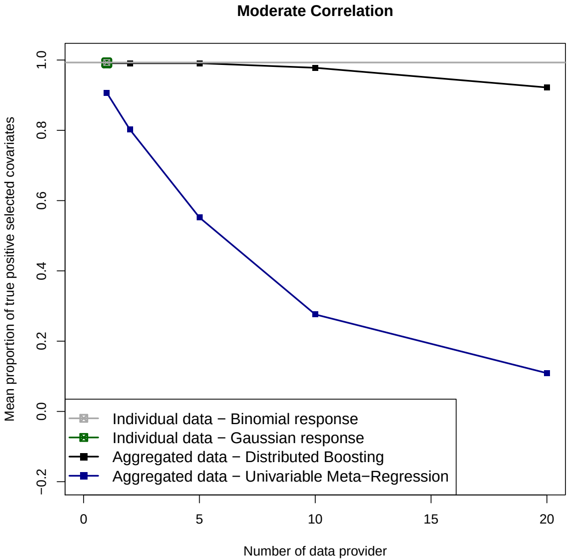
Mean proportion of true positive selected covariates

10 covariates with strong effect out of a total of 2500 covariates



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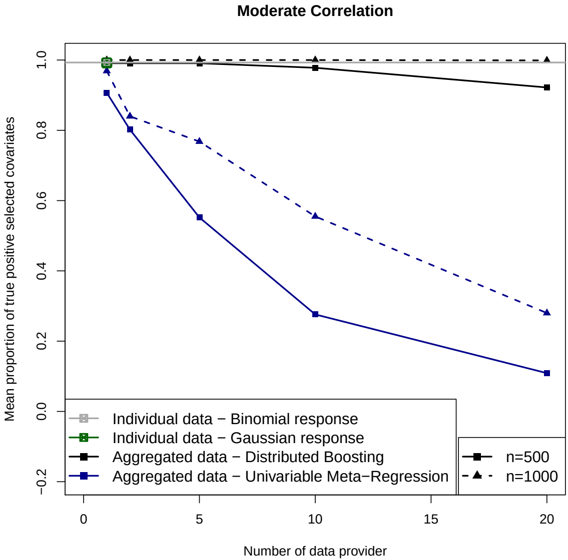

Privacy preserving approach

- Include trusted third party
  - Virtual or real
  - Set between analysis server and data provider
- Additional disassociation
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A heuristic for evaluating only some covariates[1]

	SNP 1	SNP 2	SNP 3	SNP 4	...
Step 1	$S_{1,1}$	$S_{1,2}$	$S_{1,3}$	$S_{1,4}$	...

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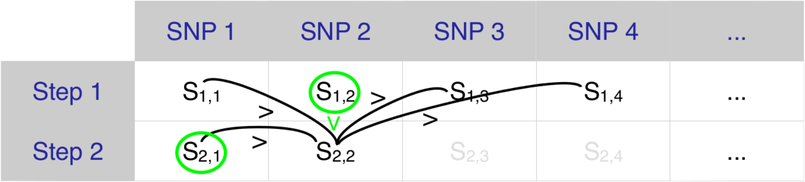

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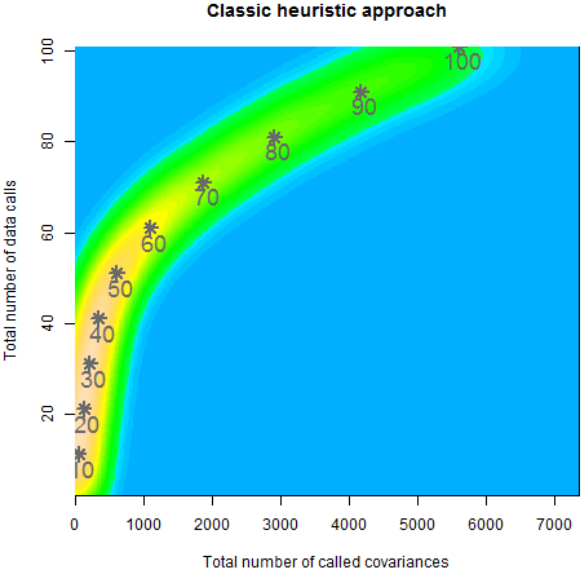

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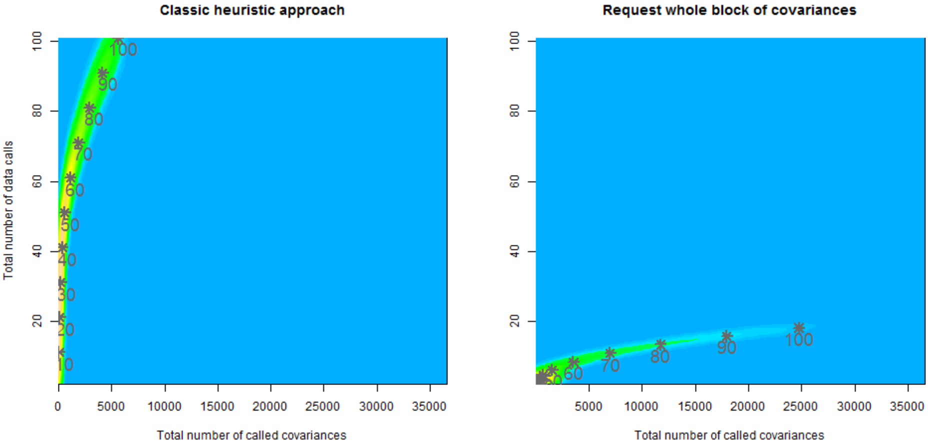

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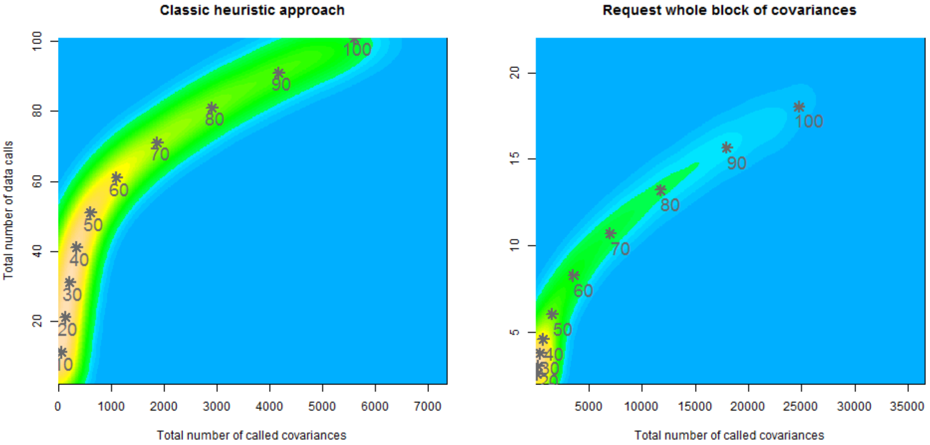

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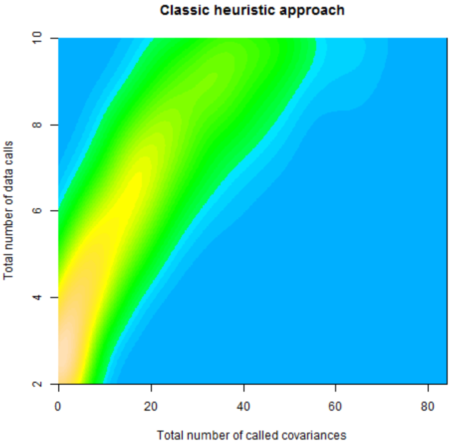

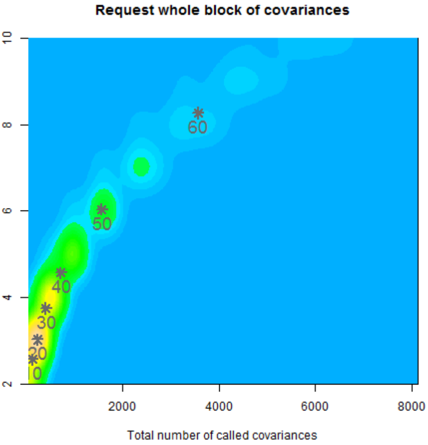

Conclusions

- Framework for high-dimensional multivariable analysis in consortia under data protection constraints
  - Result: Adequate genetic risk score
  - Only aggregated data needed
- Number and amount of data calls can be reduced
  - Release of data can be handled manually
- Automation in progress
  - Can be handled without much manpower
  - New patients can be added easily
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Contact
Daniela Zöller

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Simulation study

- Sample size: $n = 500/1000$ distributed on varying number of cohorts
- Number of covariates: $p = 2500$
- Correlation scenarios
  - Moderate correlation overall
    P(Same value for neighboring covariates)=0.5
  - Moderate correlation + groups of 5 with high correlation
    P(Same value for neighboring covariates | Diff. group) =0.5
    P(Same value for neighboring covariates | Same group) = 0.75
- Effect scenarios: Limited number of covariates with effect
  - 10 covariates with strong effect (effect size = 1)
  - 50 covariates with weak effect (effect size = 0.2)
- Number of covariates with effect per correlated group: 1 or 2
- Number of independent simulations: $M = 1000$

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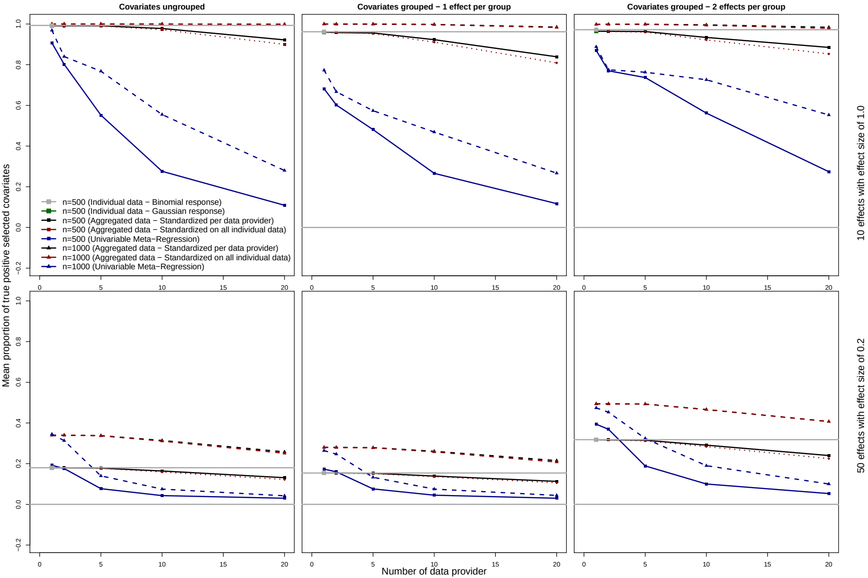

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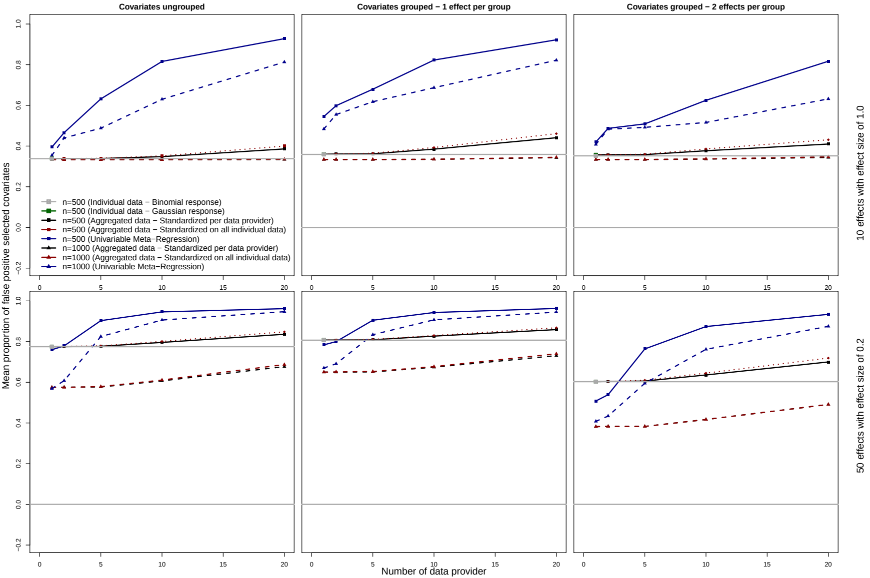
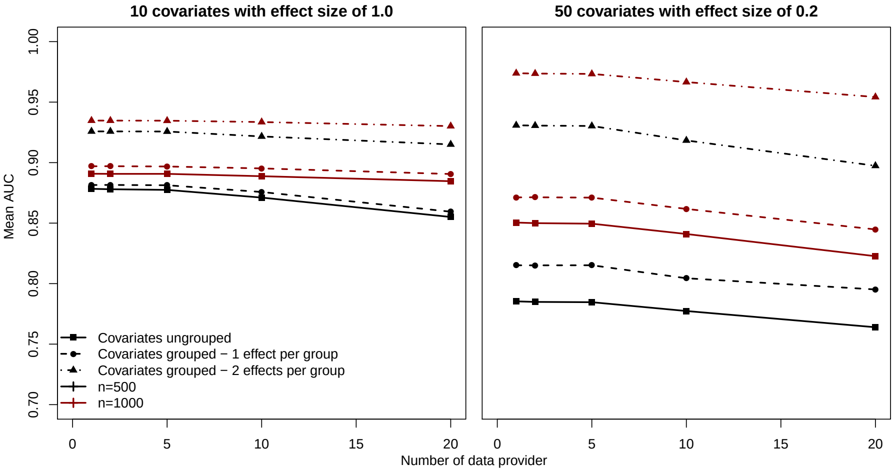


Mean AUC under ROC



Block-heuristic approach with varying buffer sizes