Stacked Clumping and Thresholding (SCT)

Making the most of C+T for polygenic scores

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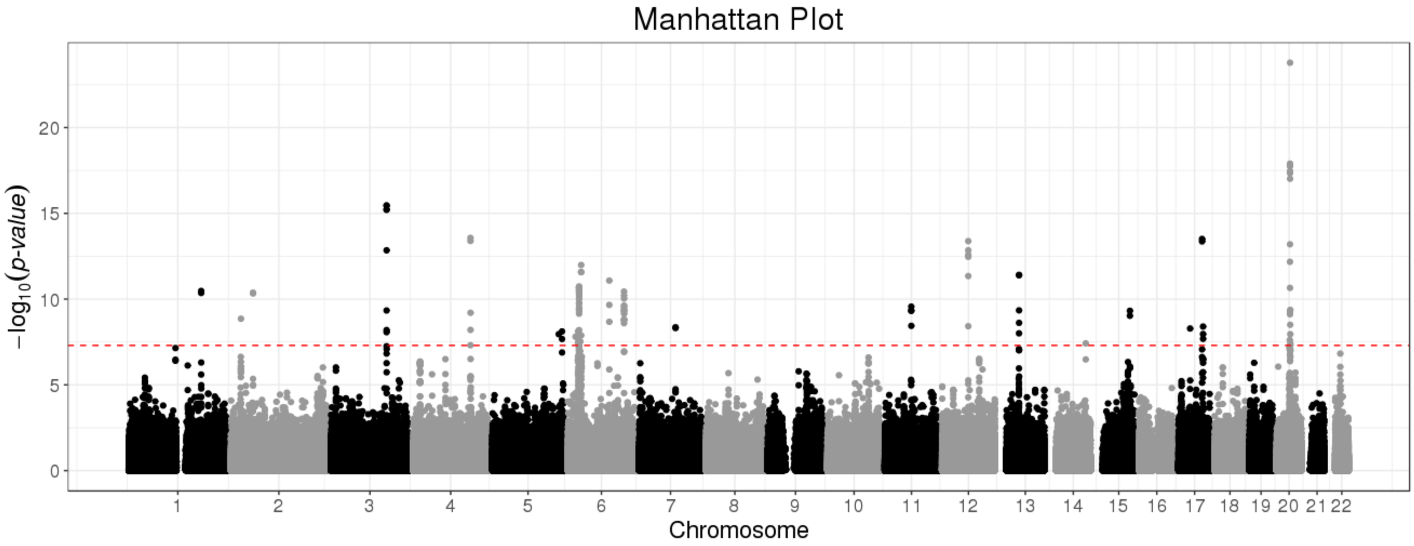
Copenhagen, June 2019

Standard PRS - part 1: estimating effects

Genome-wide association studies (GWAS)

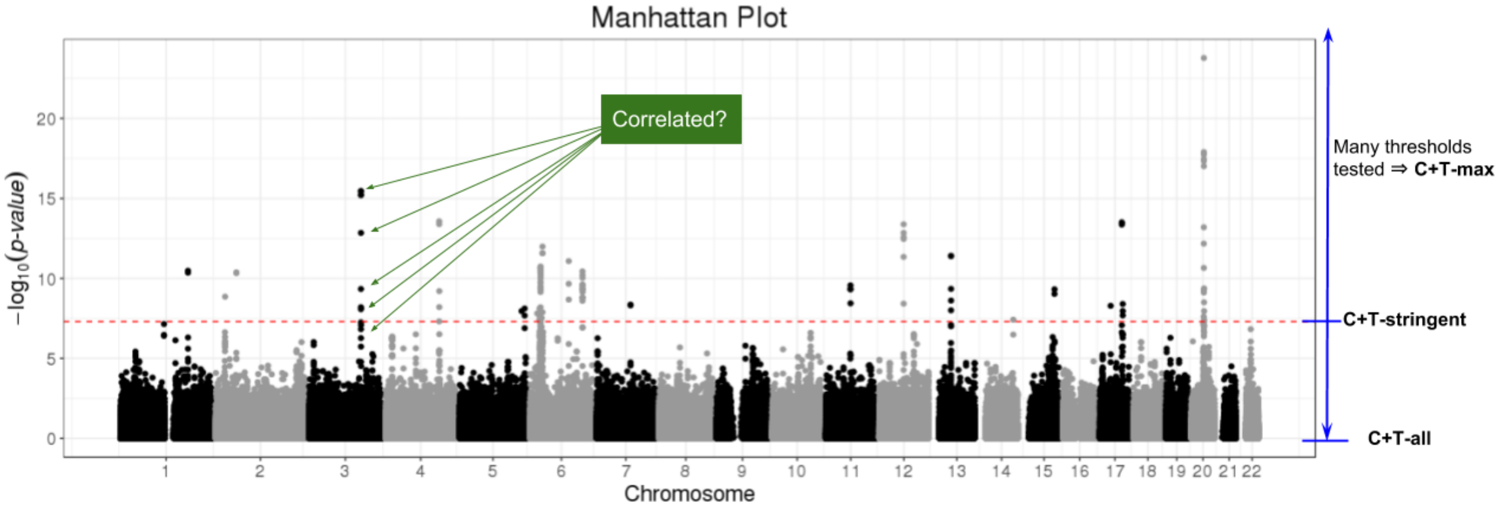
In a GWAS, each single-nucleotide polymorphism (SNP) is tested **independently**, resulting in one **effect size** $\hat{\beta}$ and one **p-value** p for each SNP.



Easy combining: $PRS_i = \sum_j \hat{\beta}_j \cdot G_{i,j}$

Standard PRS - part 2: restricting predictors

Clumping + Thresholding (C+T)



$$PRS_i = \sum_{\substack{j \in S_\text{clumping} \\ p_j < p_T}} \hat{\beta}_j \cdot G_{i,j}$$

Hyper-parameters in C+T

- threshold on squared correlation of clumping ($r_c^2 \sim 0.2$) and window size for LD computation ($w_c \sim 500kb$)

- p-value threshold (p_T between 1 and 10^{-8} and choose the best one)

- threshold of imputation quality score ($INFO_T \sim 0.3$)

$\Longrightarrow$ *stdCT* (standard C+T)

Our contribution

- an efficient implementation to compute many C+T scores for different hyper-parameters (5600 sets of hyper-parameters $\times$ 22 chromosomes)
  $\Longrightarrow$ *maxCT* (maximized C+T)

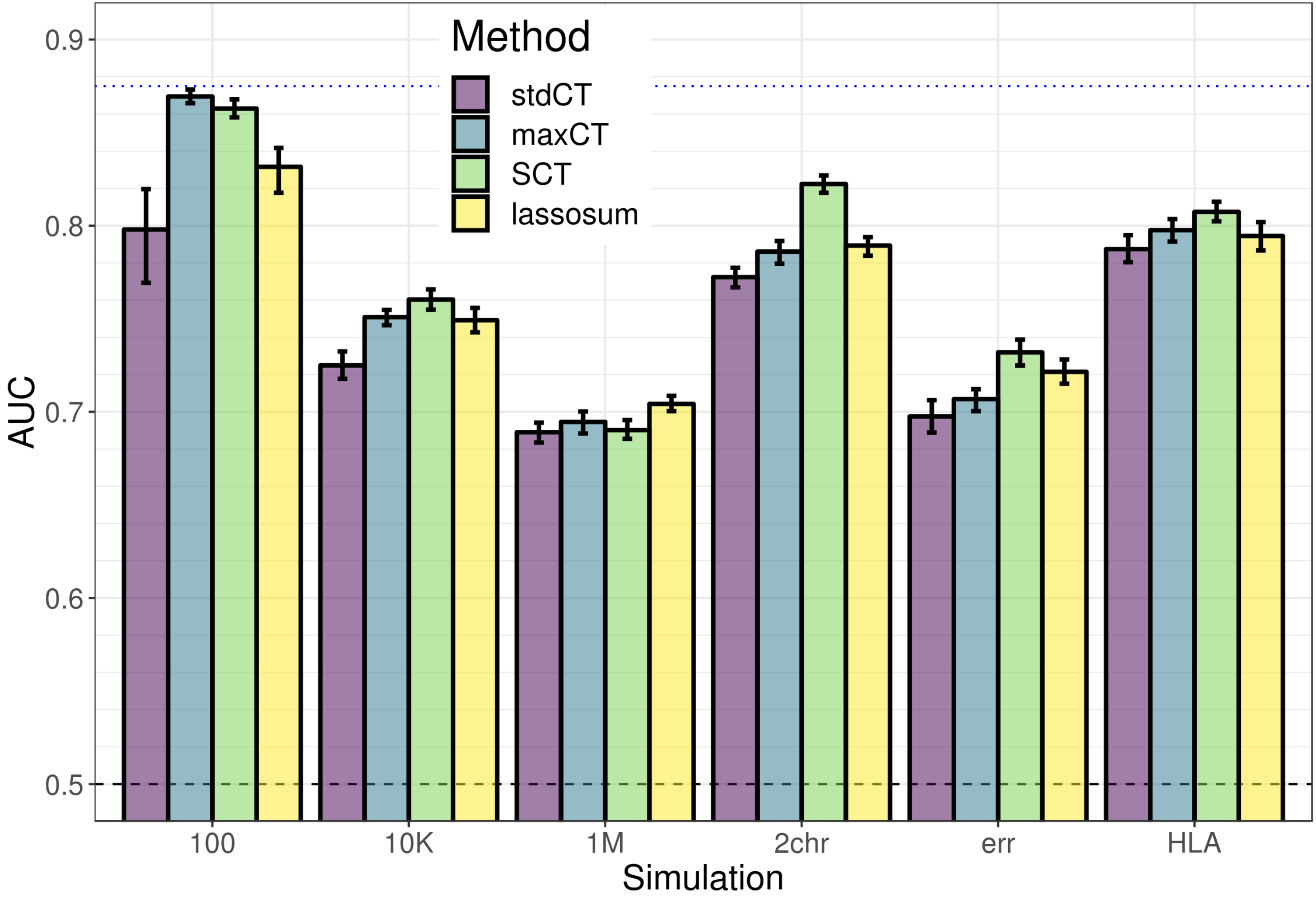
- going further by stacking all C+T models (instead of just choosing the best model)
  $\Longrightarrow$ *SCT* (Stacked C+T)

Stacking with penalized logistic regression

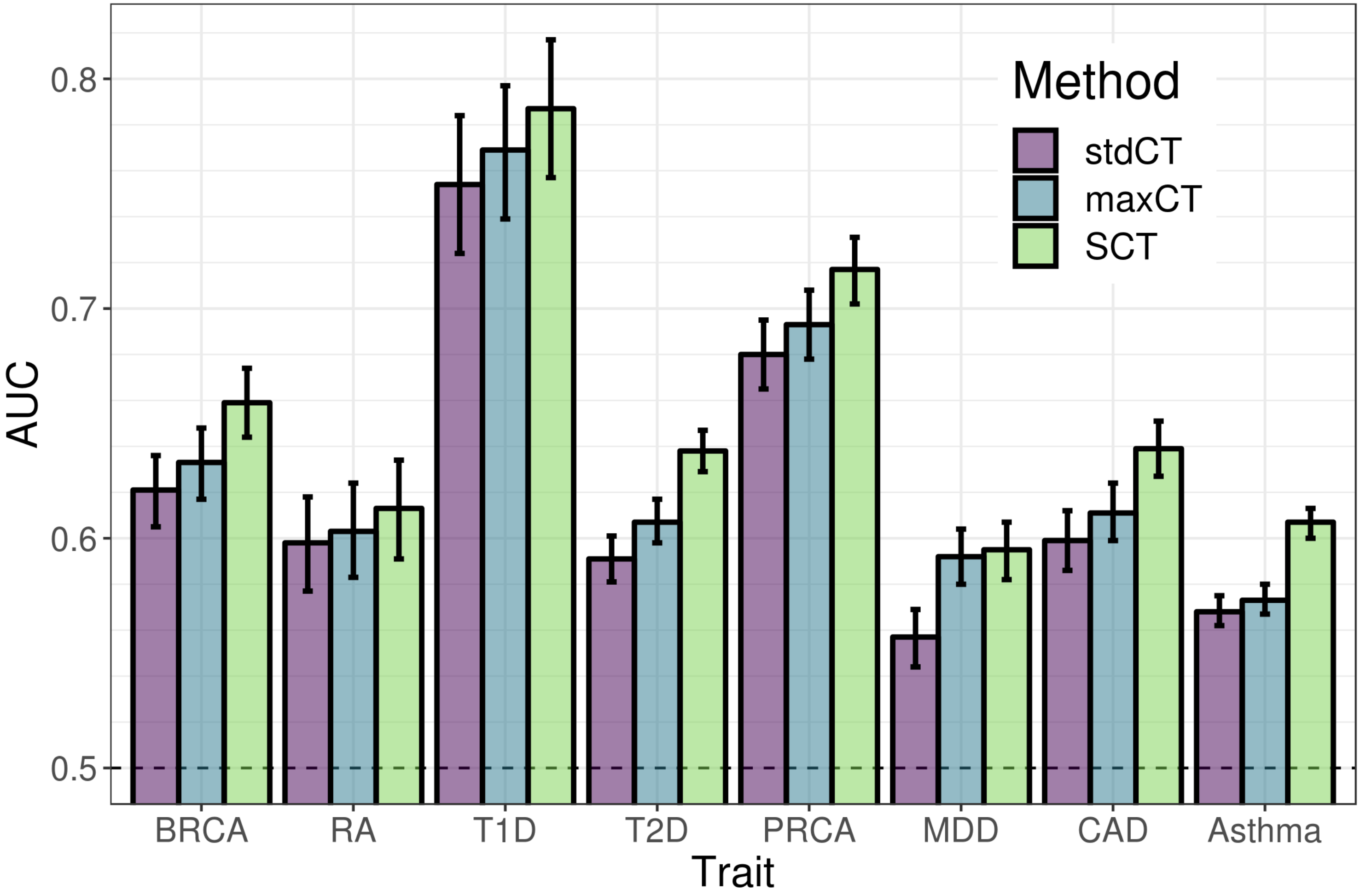
$$\underset{\beta_0,\, \beta}{\operatorname{argmin}}(\lambda, \alpha) \left\{ \underbrace{-\sum_{i=1}^{n} \left(y_i \log(p_i) + (1 - y_i) \log(1 - p_i) \right)}_{\text{Loss function}} + \underbrace{\lambda \left((1 - \alpha) \frac{1}{2} \|\beta\|_2^2 + \alpha \|\beta\|_1 \right)}_{\text{Penalization}} \right\}$$

- $p_i = 1 / \left(1 + \exp\left(-(\beta_0 + x_i^T \beta)\right)\right)$
- x is denoting the **C+T scores** and covariates (e.g. principal components),
- y is the disease status we want to predict,
- λ is a regularization parameter that needs to be determined and
- α determines relative parts of the regularization $0 \le \alpha \le 1$.

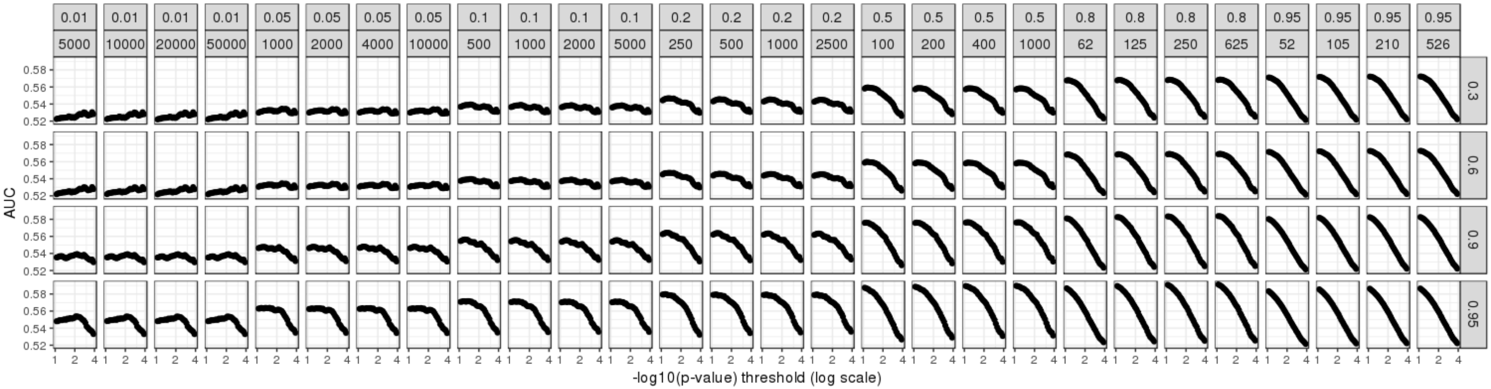
Results (simulations)

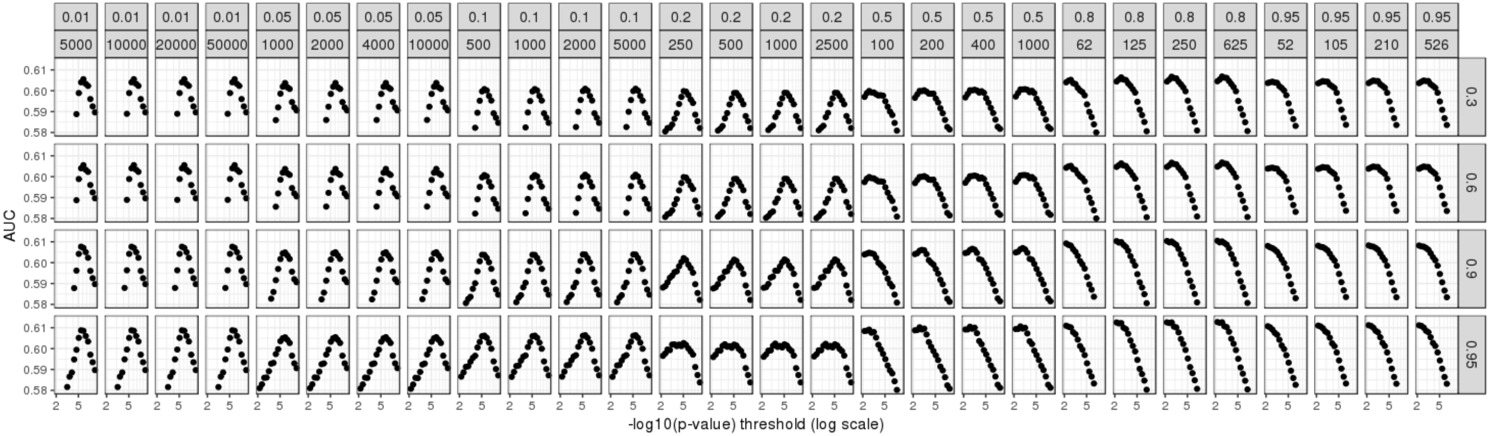


Results (real data)



Results (grid of hyper-parameters for MDD and T2D)





Beyond predicting one disease

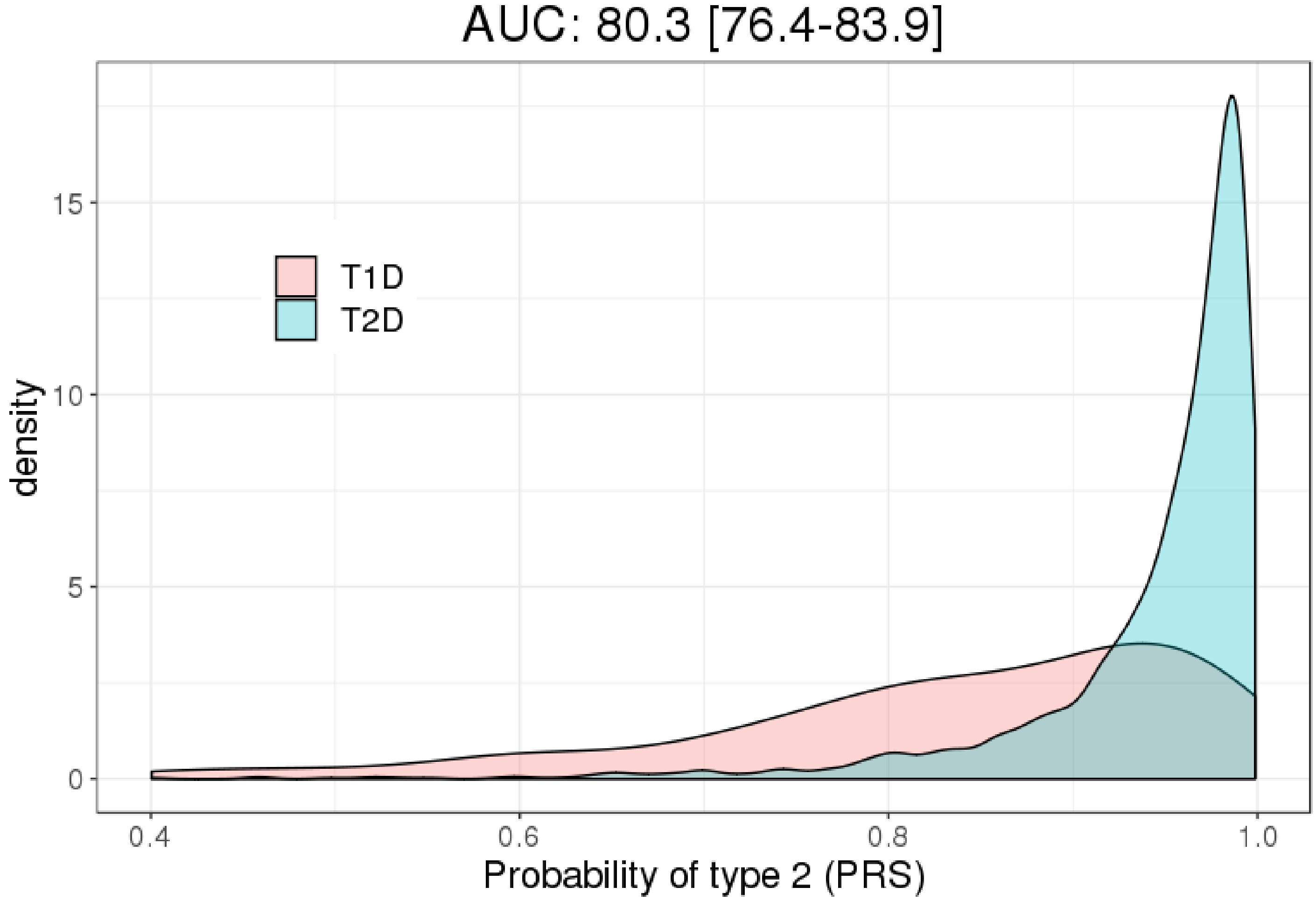
Differentiating type 1 from type 2 diabetes

Stacking C+T scores for both types of diabetes

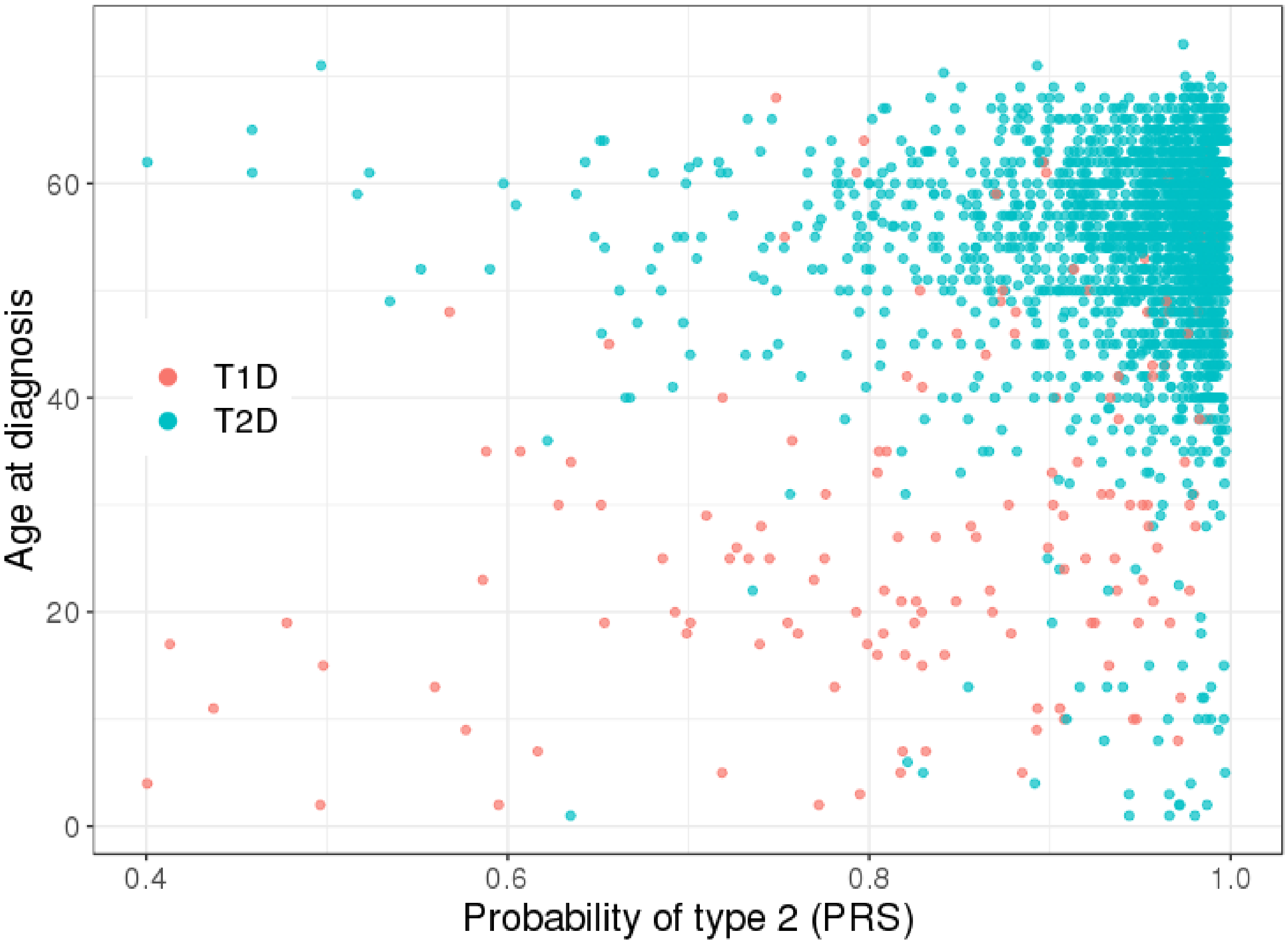
$$\underset{\beta_0,\,\beta}{\operatorname{argmin}}(\lambda, \alpha) \left\{ \underbrace{-\sum_{i=1}^{n} \left(y_i \log(p_i) + (1 - y_i) \log(1 - p_i)\right)}_{\text{Loss function}} + \underbrace{\lambda \left((1 - \alpha) \frac{1}{2} \|\beta\|_2^2 + \alpha \|\beta\|_1 \right)}_{\text{Penalization}} \right\}$$

- $p_i = 1/\left(1 + \exp\left(-(\beta_0 + {x_1}_i^T \beta_1 + {x_2}_i^T \beta_2)\right)\right)$
- x_1 is denoting the C+T scores derived from **T1D** summary statistics
- x_2 is denoting the C+T scores derived from **T2D** summary statistics
- y (restricting to people with diabetes) is
  - 1 for type 2 diabetes and
  - 0 for type 1 diabetes

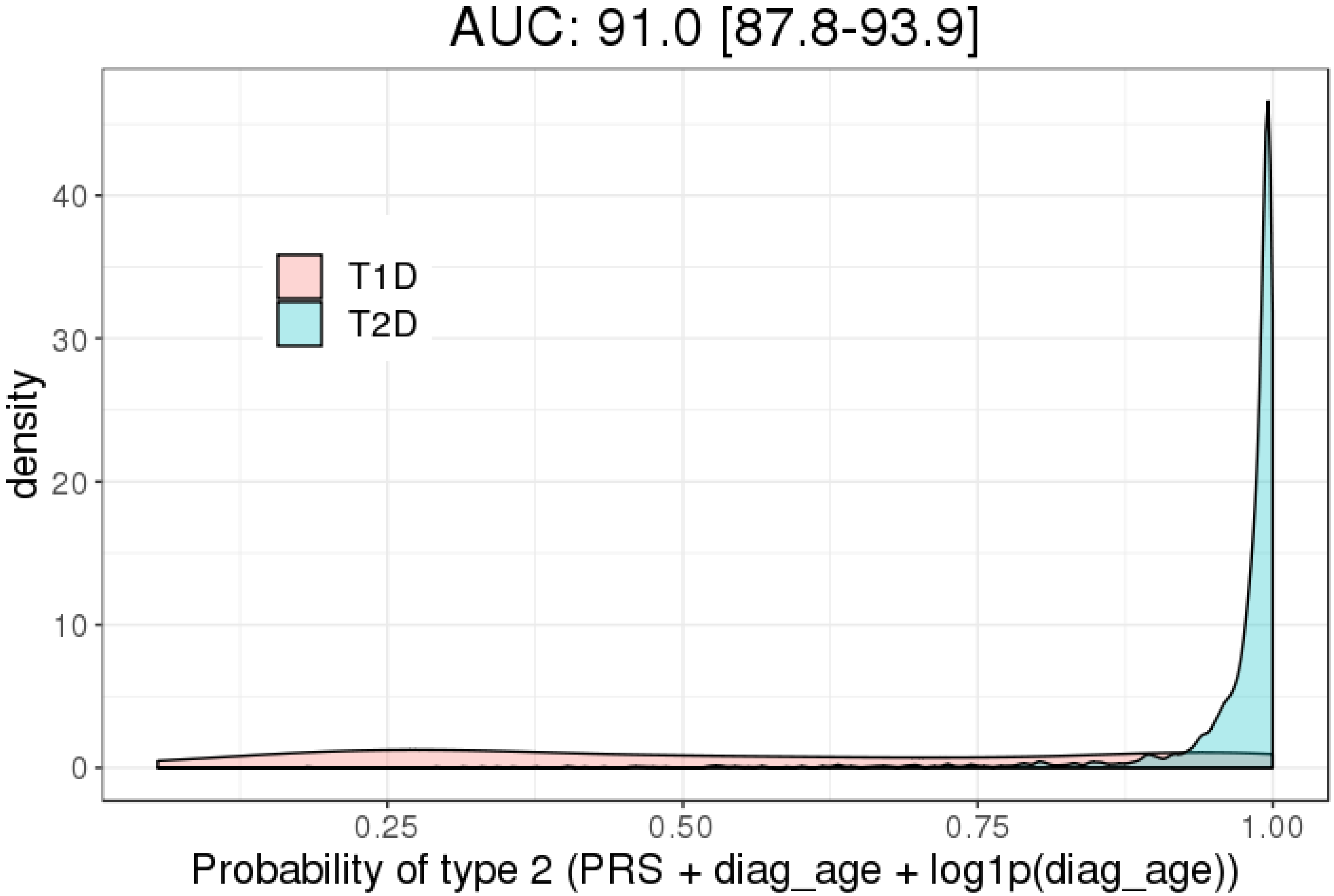
Predictive power of PRS



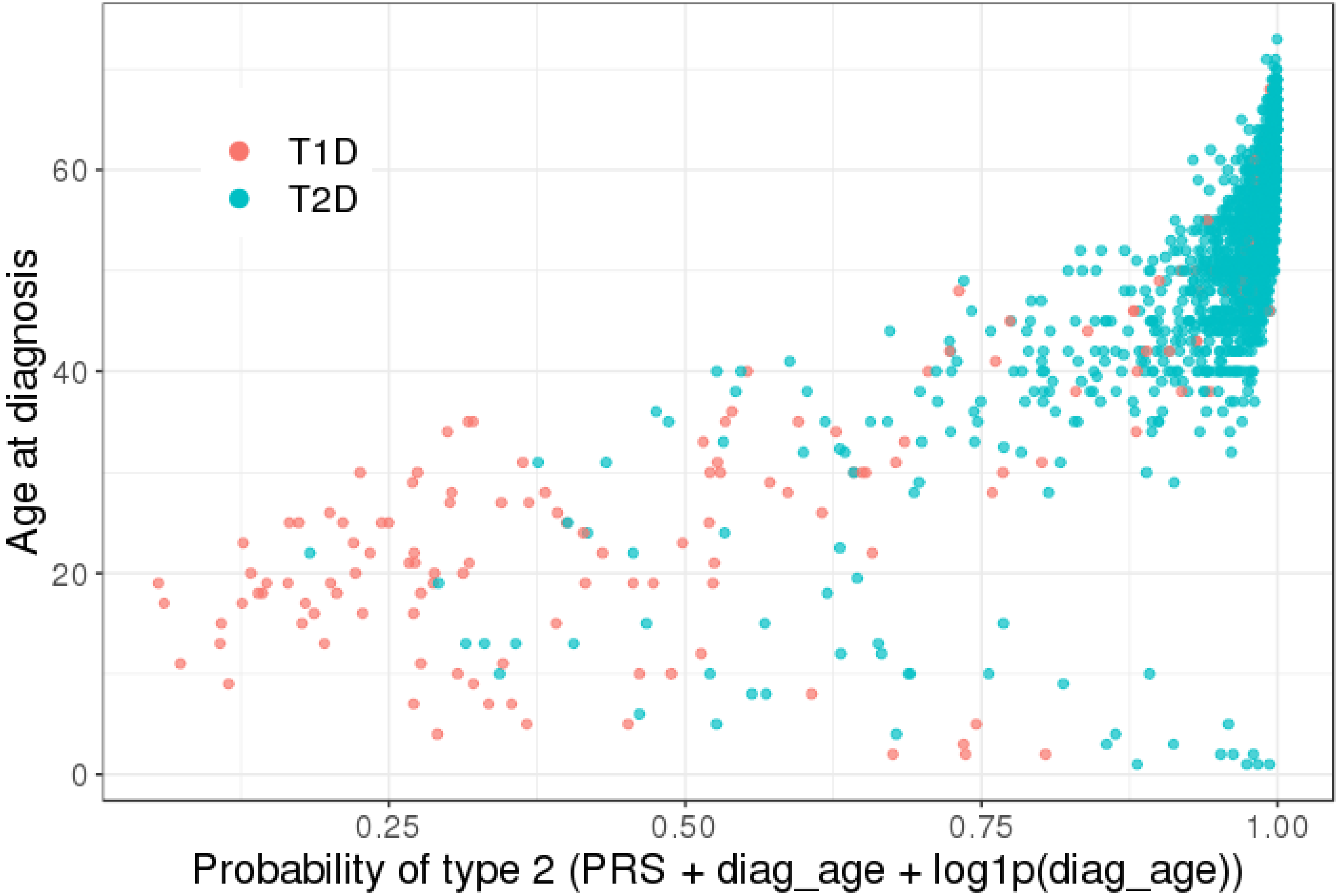
Investigating age of diagnosis



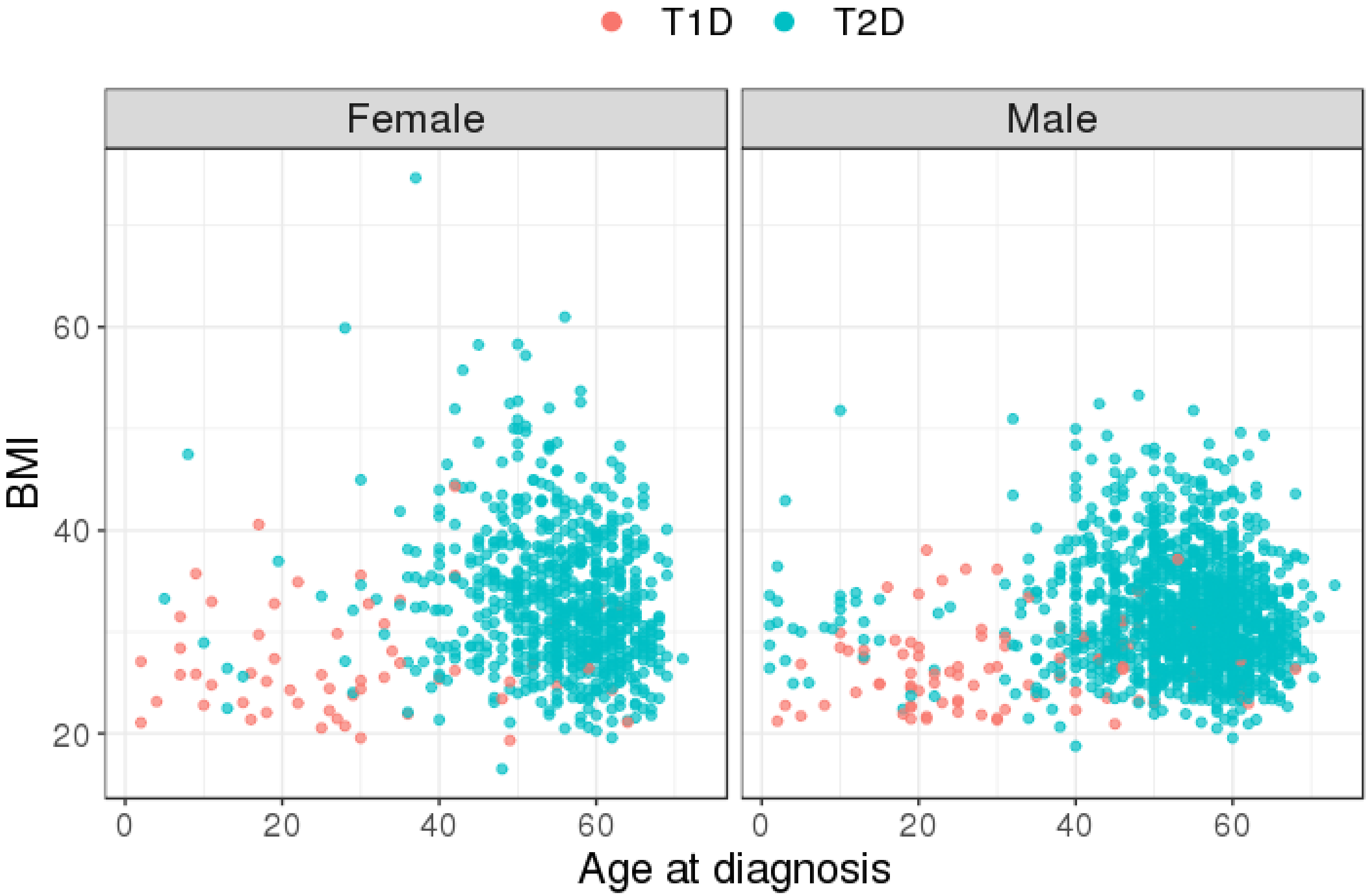
Predictive power of PRS + age at diagnosis



Investigating age of diagnosis



Other useful variables?



Conclusion / limitations

- PRS is of relative improvement over "age at diagnosis" alone
  (AUC of 91.0 [87.8-93.9] vs 88.7 [85.1-92.0])

- Small sample size
  (493 T1D / 7507 T2D in training and 149 / 2139 in test set)

- Use of other variables?
  (available at diagnosis: BMI, sex, others?)

- Consider other types of diabetes?

- Possible misdiagnosis errors in the dataset used

- Try a different method?

  - build one PRS for each type of diabetes separately
    and merge them after with other variables?

  - prefer individual-level data methods?
    (works best for T1D because of large effects in HLA region)

Thanks!

Presentation available at

https://privefl.github.io/thesis-docs/SCT-diabetes.html

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Slides created via R package **xaringan**.