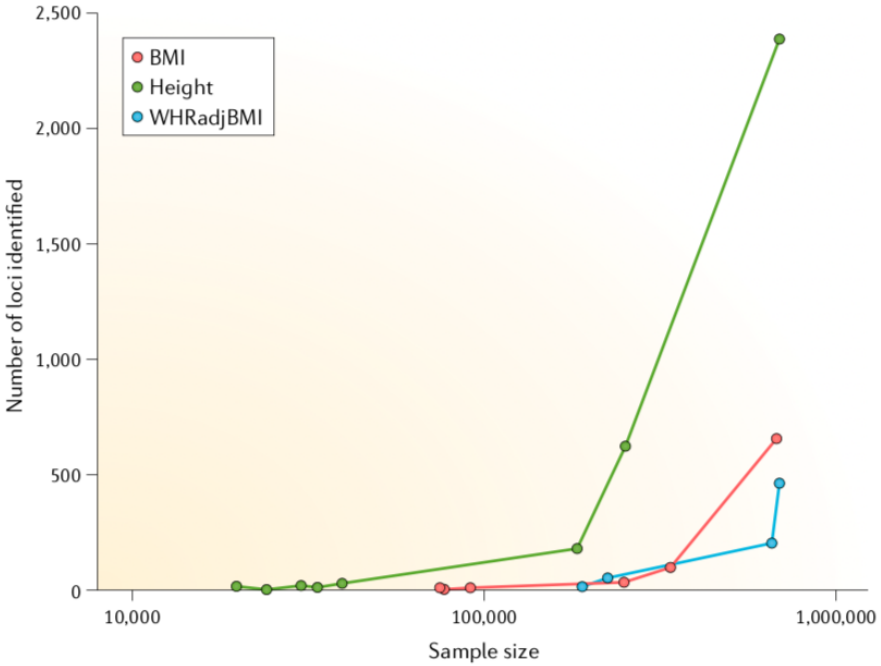
What drives the reduced prediction accuracy of polygenic scores in non-European individuals?

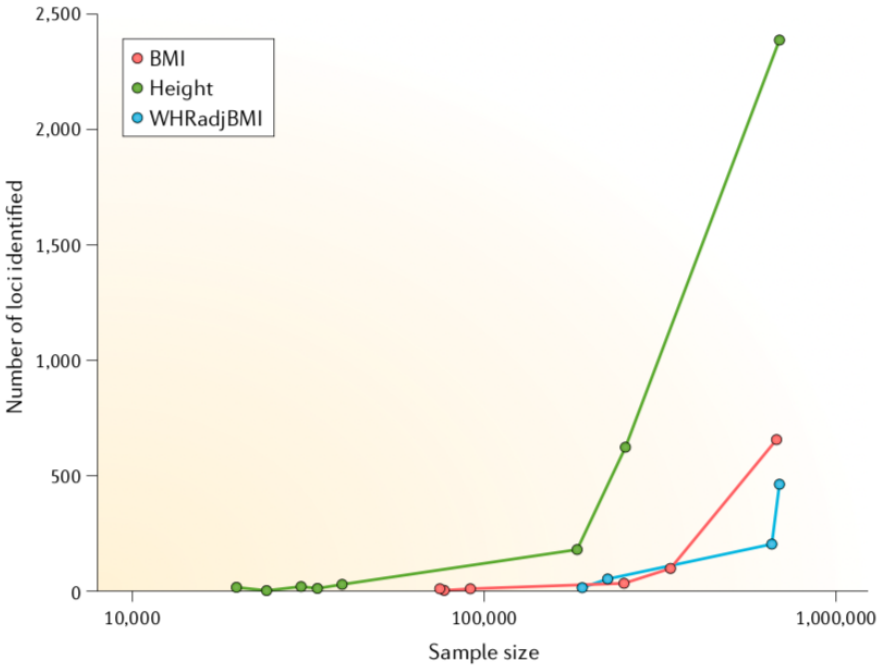
Bárbara Domingues Bitarello

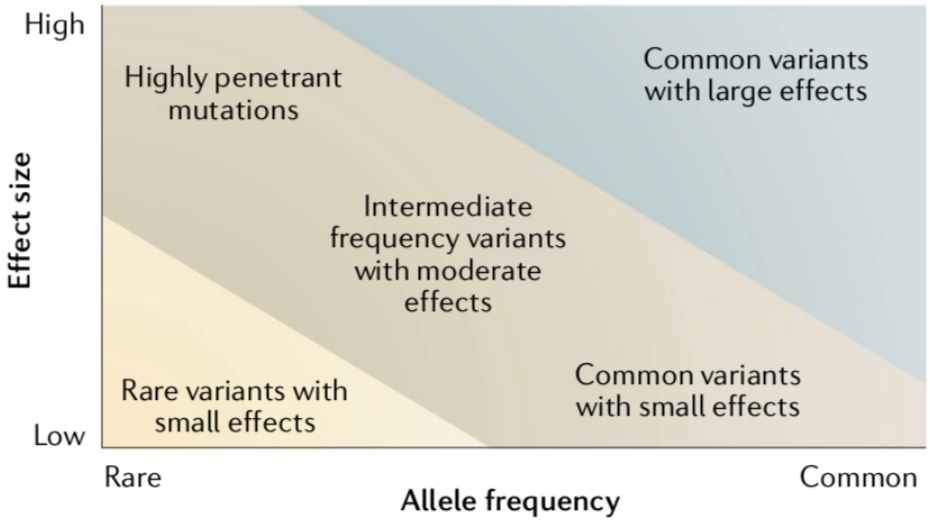
Perelman School of Medicine, University of Pennsylvania

Many variants



Many variants with small effect size





[Tam et al. (2019) *Nat Rev Genet*]

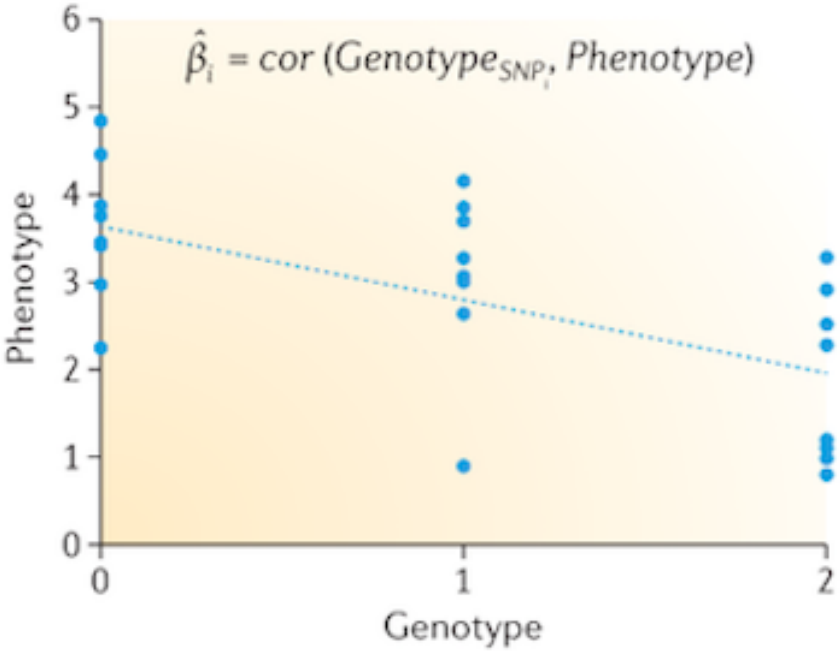
Combined, they explain a lot!

Some examples

Phenotype	Statistic	Value	Variants
height	R-squared	25.0	3000
schizophrenia	R-squared	7.0	100
ADHD	R-squared	5.5	100
breast cancer	AUC	60.0	1000
cardiovascular disease (CAD)	AUC	81.0	6000

PS: In Europeans...

Polygenic risk scores add up those small effects



Pasaniuc & Price (2017), *Nat Rev Genet*

$$PRS = \sum_{i=1}^{m} \hat{\beta}_i G_{j,i}$$

$\hat{\beta}$: effect size (from GWAS)

G : Effect allele dosage

j: Individuals

i: SNPs

independence

additive model

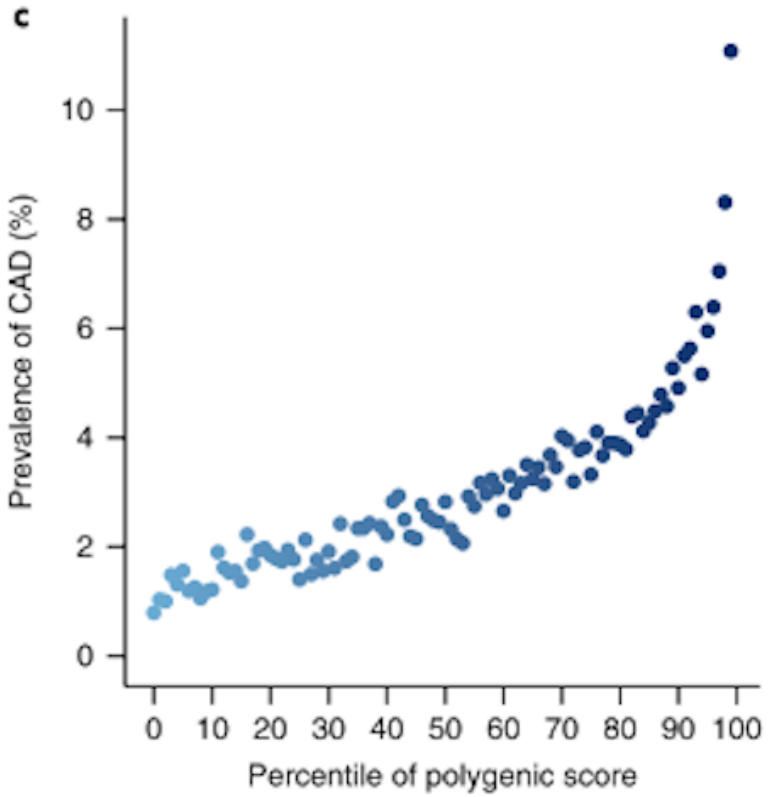
PRSs are appealing

easy

promising

fast

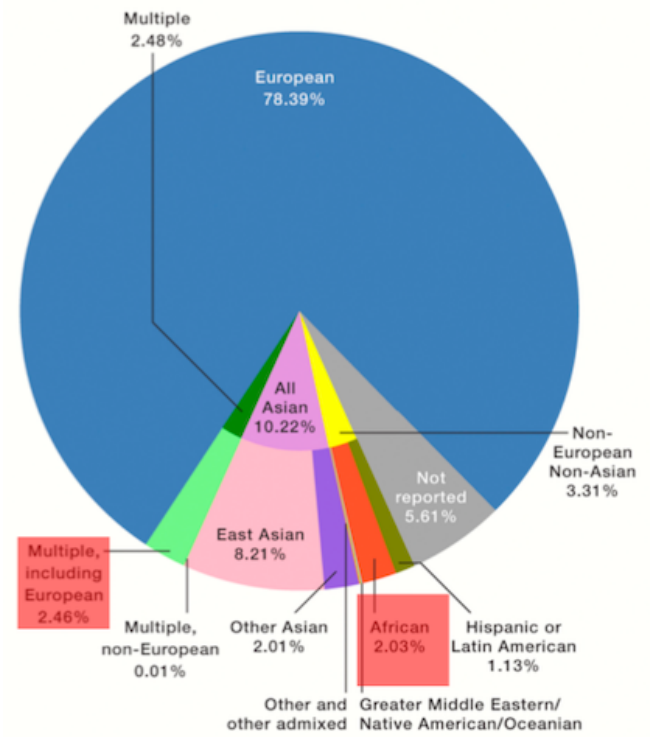
minimal requirements



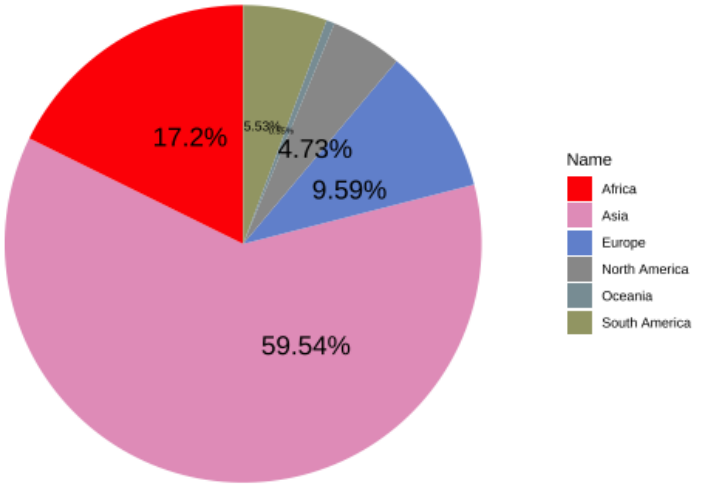
[Khera et al (2018) Nat Genet]

What about ancestry?

European ancestry represent almost 80% of GWAS participants...



[Sirugo, Williams & Tishkoff (2019) *Cell*]

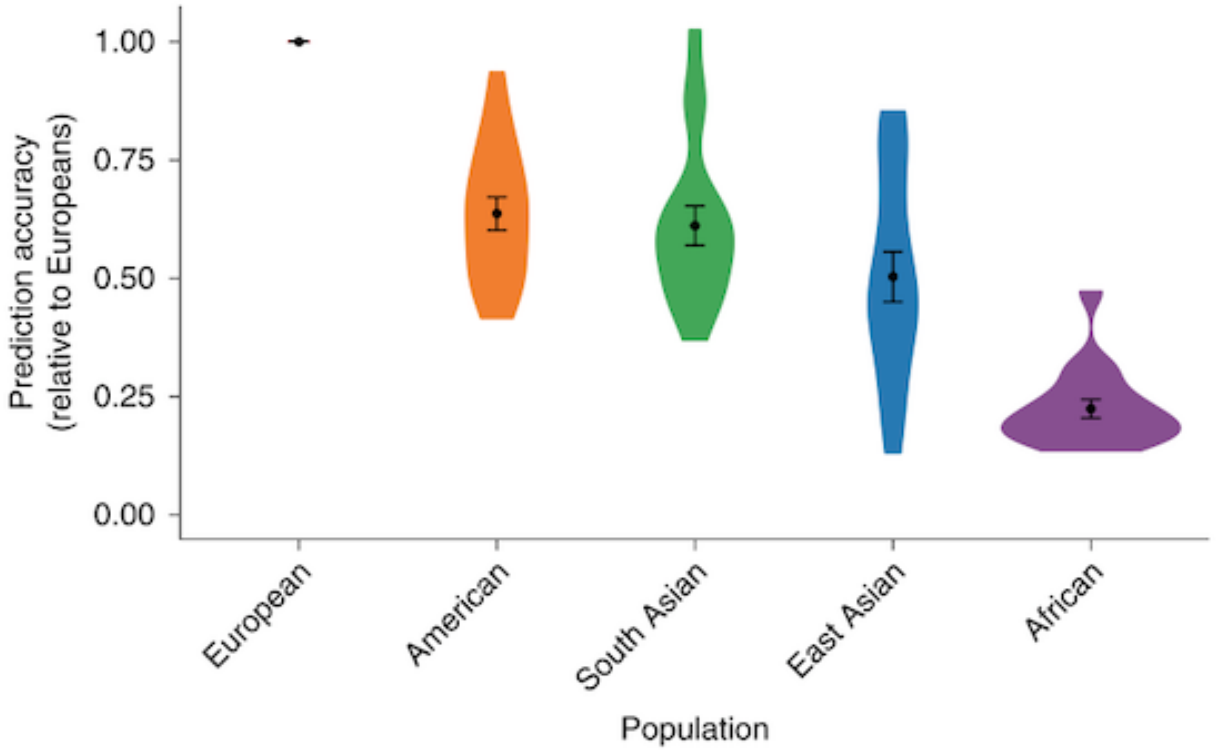


[Data: https://worldpopulationreview.com/]

.. and <15% of the world's population

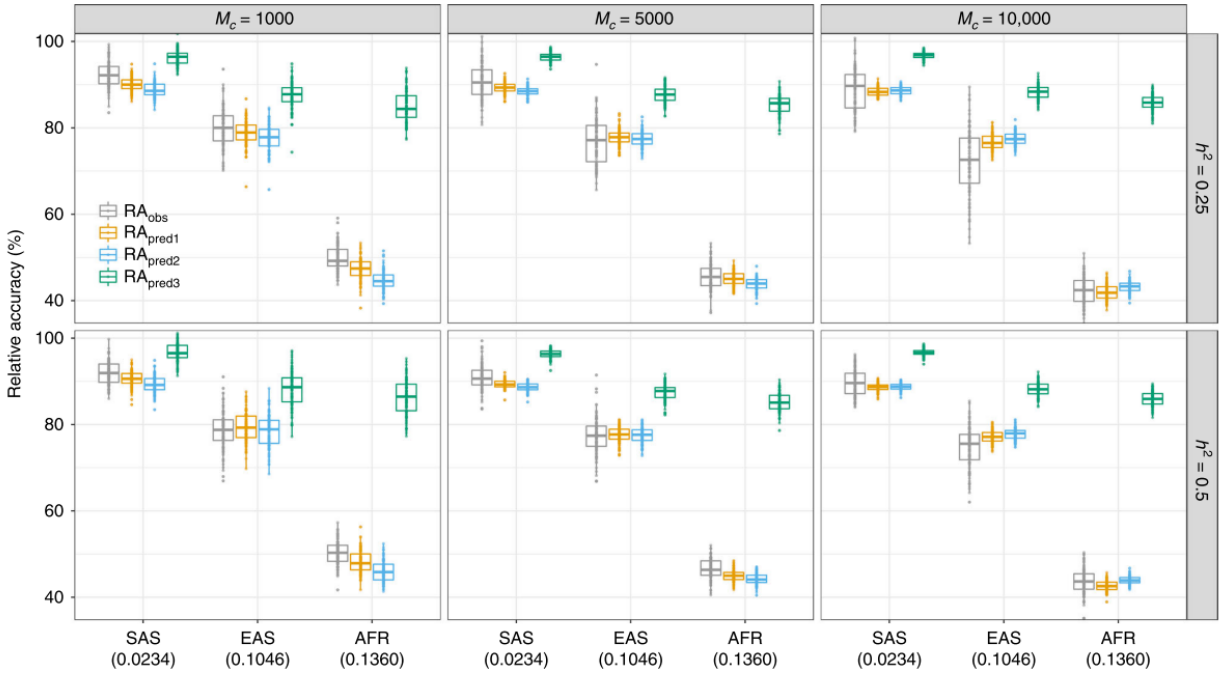
How does PRS accuracy transfer across ancestries?

PRS accuracy decreases with genetic distance from Europeans



[Martin et al. (2019) *Nat Genet*]

PRS accuracy decreases with genetic distance from Europeans



[Wang & Wisscher (2020) *Nat Comms*]

LOA: loss of accuracy

Why is this loss of prediction observed?

What **can** ***we do*** about it?

Many factors may influence LOA

causal variants

local selection

gene-gene interactions

gene-environment interactions

marginal effect sizes

LD

site frequency spectrum

phenotypic variance

These factors are not mutually exclusive!

Questions

How do these different factors affect prediction accuracy?

Can we leverage ancestry into the PRS and improve predictions?

Let's look at height

Ancestry as a continuous variable

highly polygenic

many cohorts phenotyped

large GWAS (UKBB

$\sim$ 360,000 Europeans)

$$height \sim Sex + Age + Age^2 + p_{eur}$$

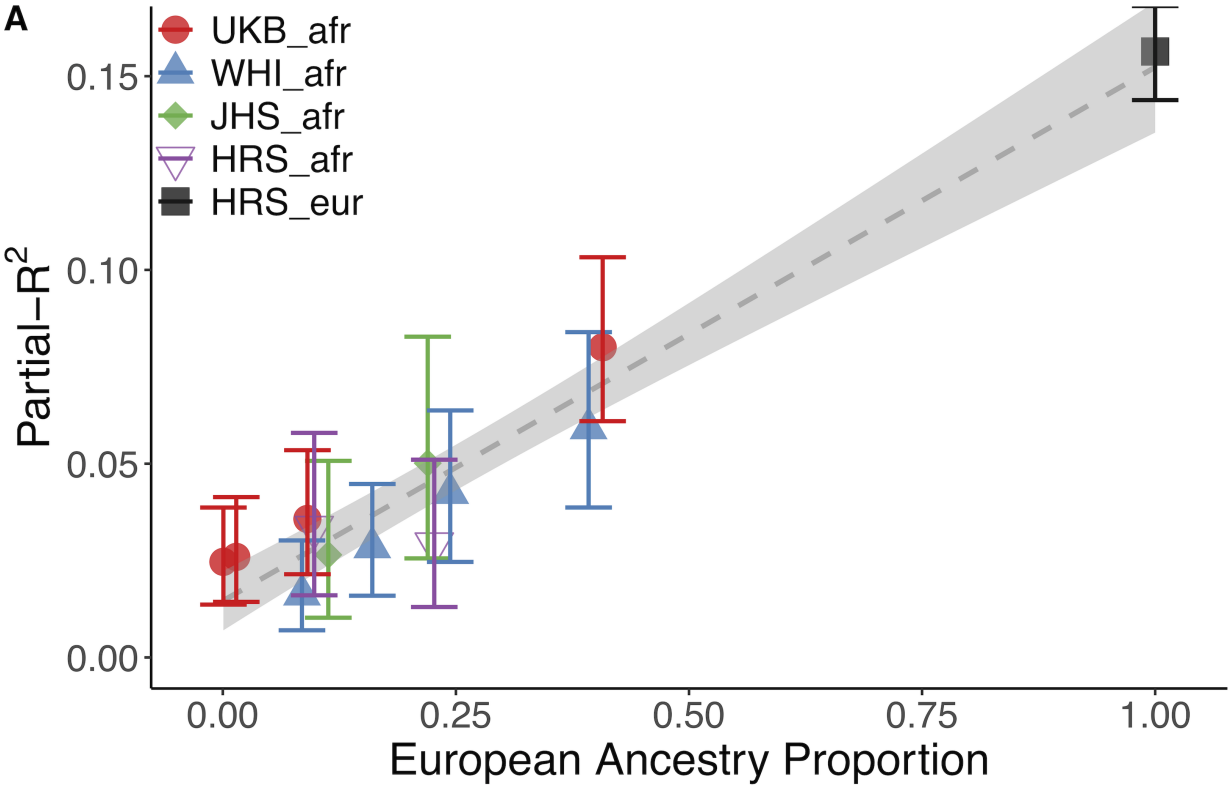
$$height \sim Sex + Age + Age^2 + p_{eur} + PRS$$

European + African ancestry

Data	Ancestry	N	Number_SNPs
UKBB_eur	European	9998	685475
HRS_EUR	European	10159	1511742
UKBB_afr	African + European	8700	685475
WHI_afr	African American	6863	741983
JHS_afr	African American	1773	702685
HRS_afr	African American	2251	1511742

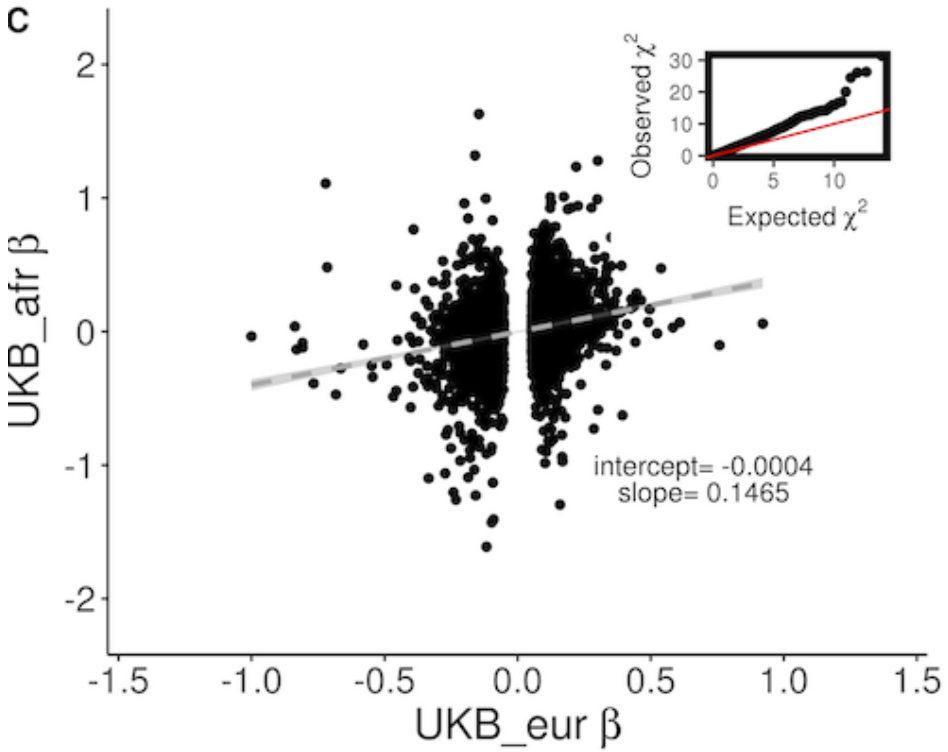
[Bitarello & Mathieson (2020), *G3*]

PRS accuracy increases with proportion of European ancestry



[Bitarello & Mathieson (2020), *G3*]

GWAS from UKBB (AFR) individuals



$$y = sex + age + age^2 + 10PCs$$

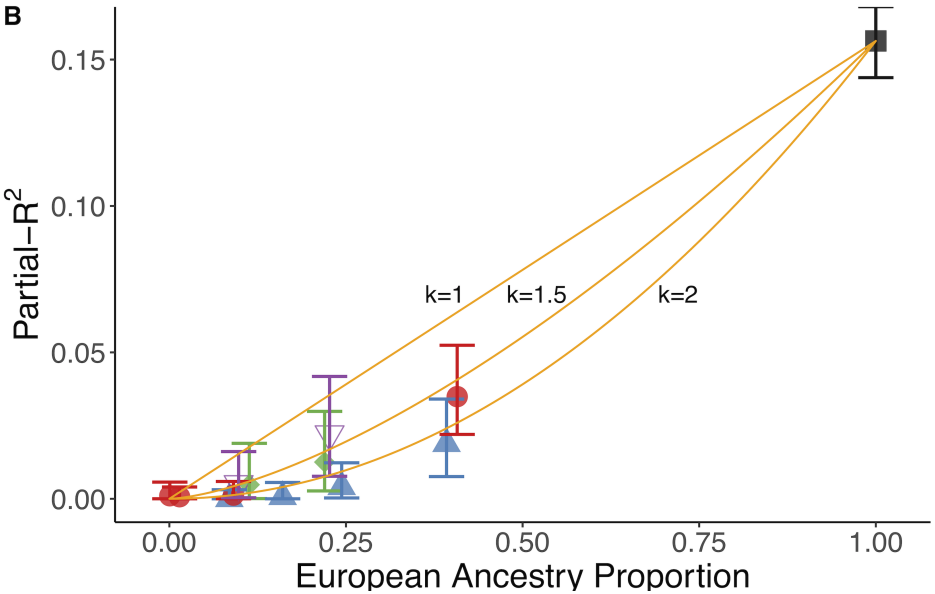
$$N_{AFR} \sim 8,800$$

$$N_{EUR} \sim 350,000$$

$$\chi^2_{diff} = \left[\frac{\beta_{eur} - \beta_{afr}}{\sqrt{SE^2_{eur} + SE^2_{afr}}} \right]^2$$

[Bitarello & Mathieson (2020), *G3*]

Using only EUR chunks of each genome



[Bitarello & Mathieson (2020), *G3*]

$$y = 0.15p_{eur}^{k}$$

$k = 1$

all predictive power comes from European chunks

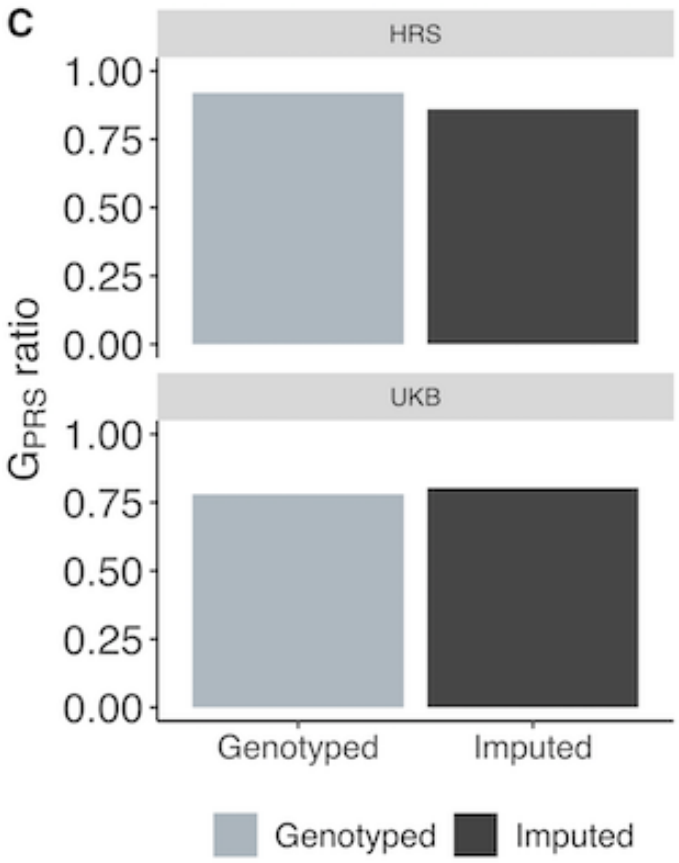
$k = 2$

predictive power is uniformly distributed

Surprisingly, this relationship seems to be more like k=2

Others found that the LOA can be fully recovered by including EUR chunks [Marnetto et al. (2020) *Nat Comms*]

Allele frequency differences explain up to 20% of LOA



Additive genetic variance

$$G_{PRS} = \frac{\sum 2f_{i_afr}(1 - f_{i,afr})\beta^2_{i,eur}}{\sum 2f_{i,eur}(1 - f_{i,eur})\beta^2_{i,eur}}$$

[Bitarello & Mathieson (2020), *G3*]

Prediction: variance in phenotype lower in EUR

genome-wide genetic variance in EUR is $\sim 76\%$ of that in AFR

$$height \sim Sex + Age + Age^2 + p_{eur}$$

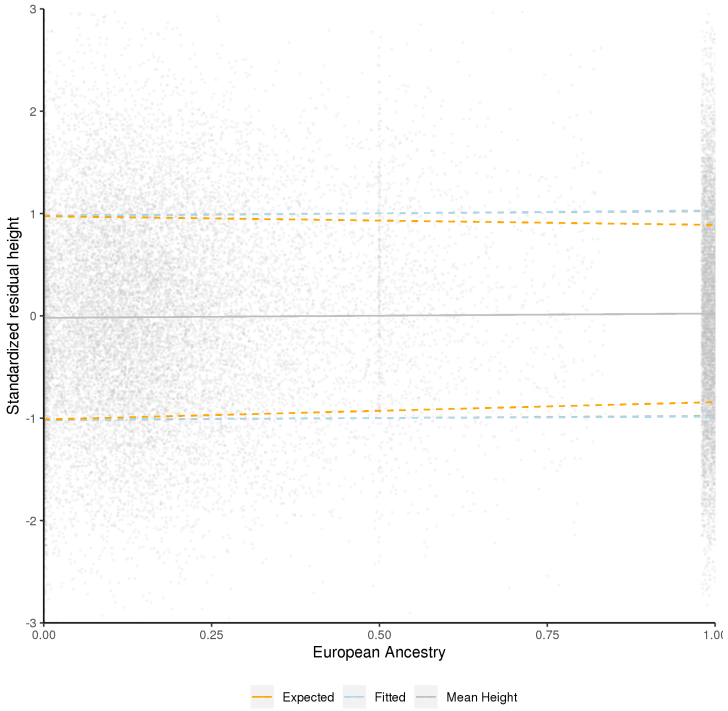
Variable variance model:

$$y = \mu + \beta p_{j,eur} + \epsilon; \epsilon_j \sim N(0, \delta^2 + \gamma p_{j,eur})$$

Mean+1 1sd, constant variance

fitted, variable variance

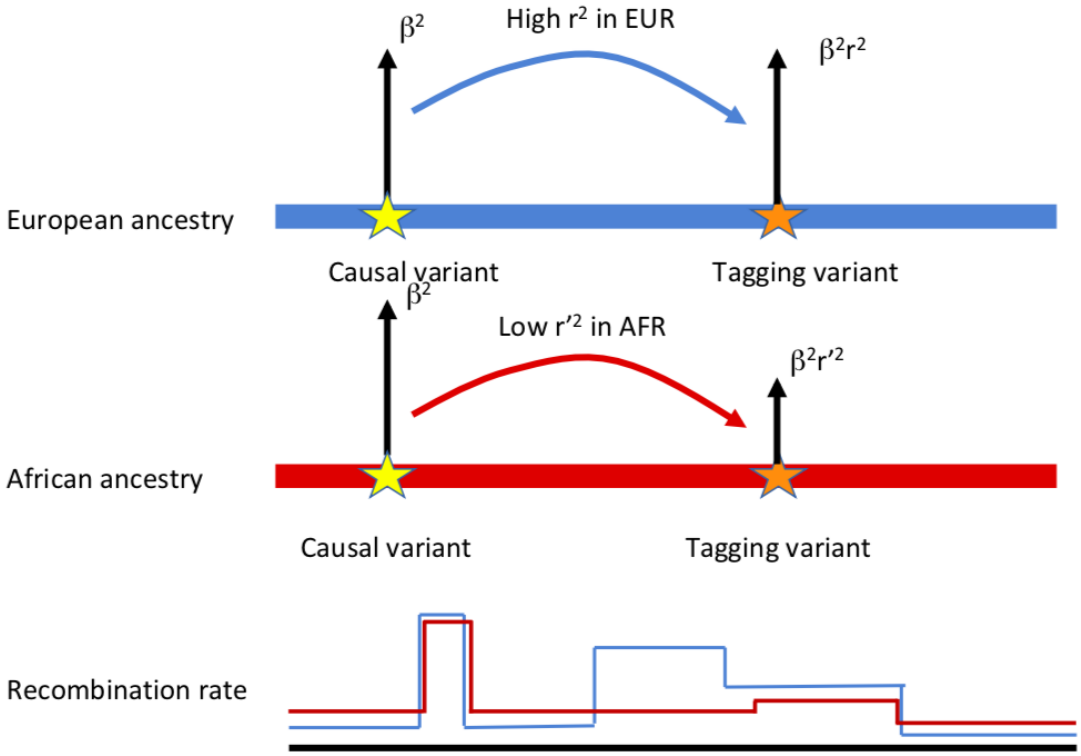
model, variance in phenotypic variance is 100% in AFR and 76% in EUR



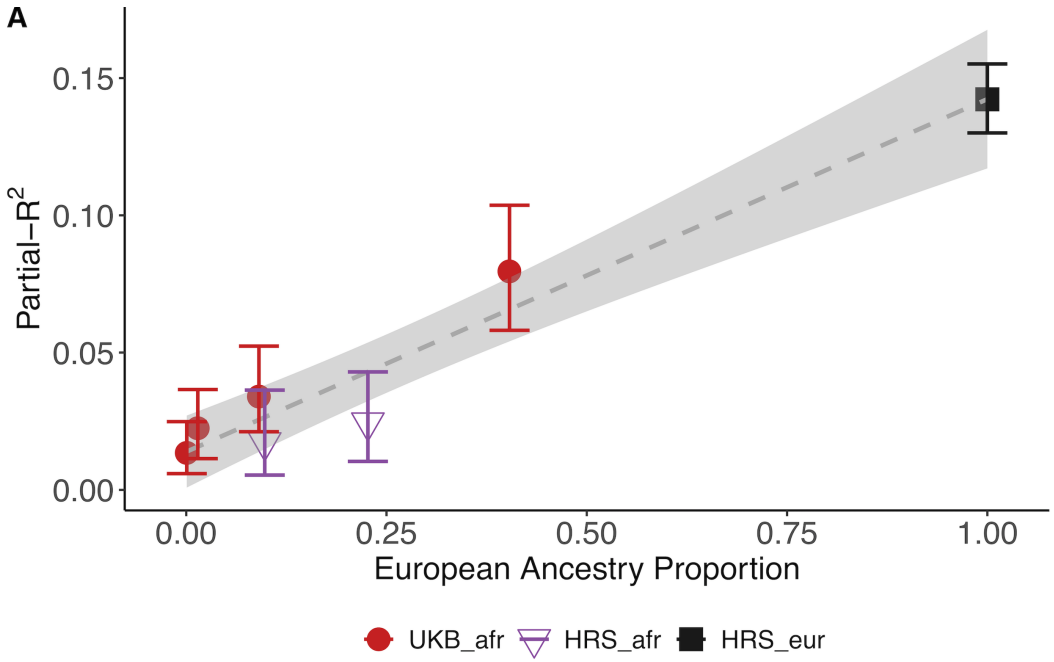
[Bitarello & Mathieson (2020), *G3*]

Observation: Phenotypic variance does not change with ancestry

Differences in linkage disequilibrium



Prediction: better tagging of causal variants decreases LOA

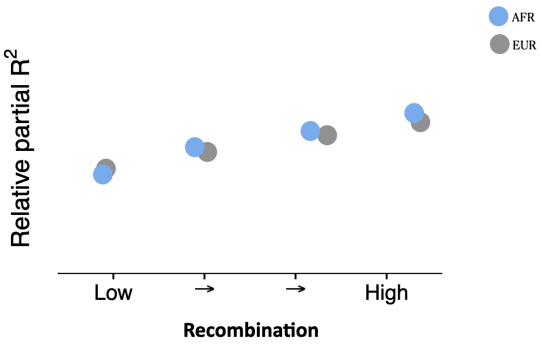


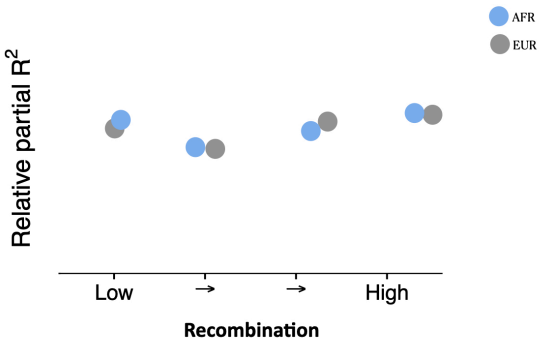
[Bitarello & Mathieson (2020), *G3*]

Observation: Imputation doesn't influence LOA

Prediction 1: LOA is independent of LD differences

$$Rel_{R2} = \frac{R^2_{bin}}{R^2_{total}}$$

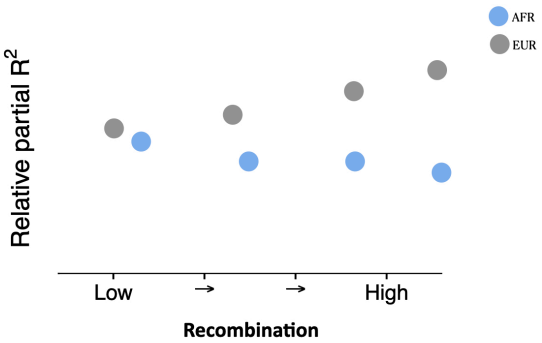


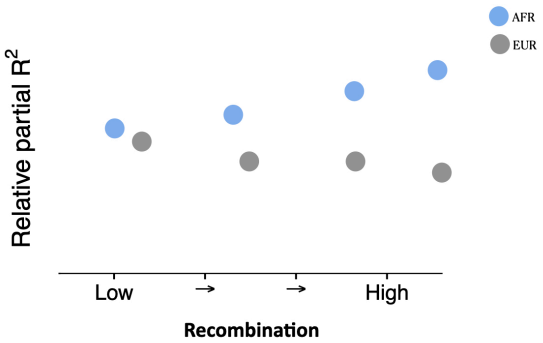


Similar slopes

Prediction 2: LOA is dependent of LD differences

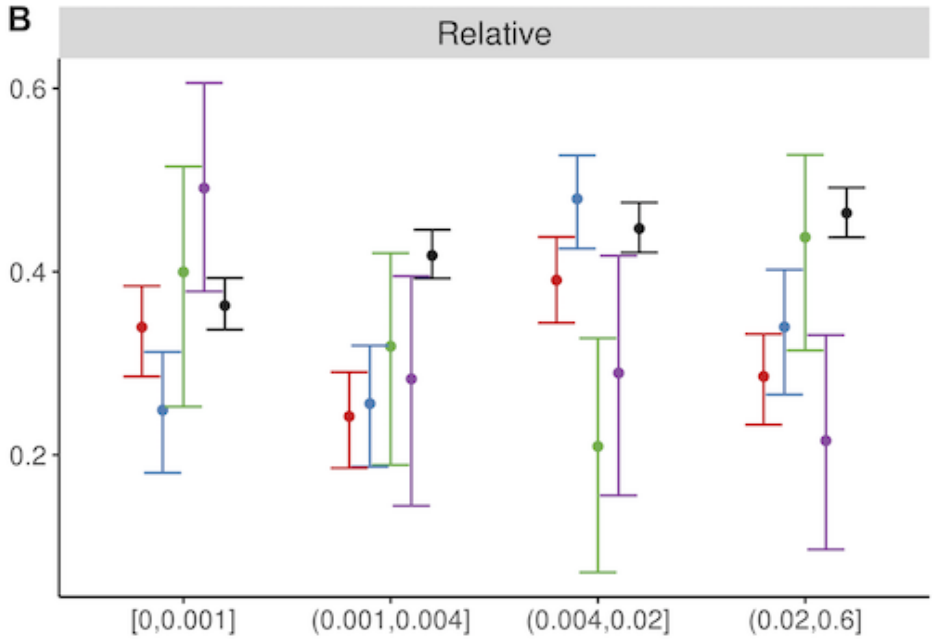
$$Rel_{R2} = \frac{R^2_{bin}}{R^2_{total}}$$





Different slopes

$$Rel_{R2} = \frac{R^2_{bin}}{R^2_{total}}$$

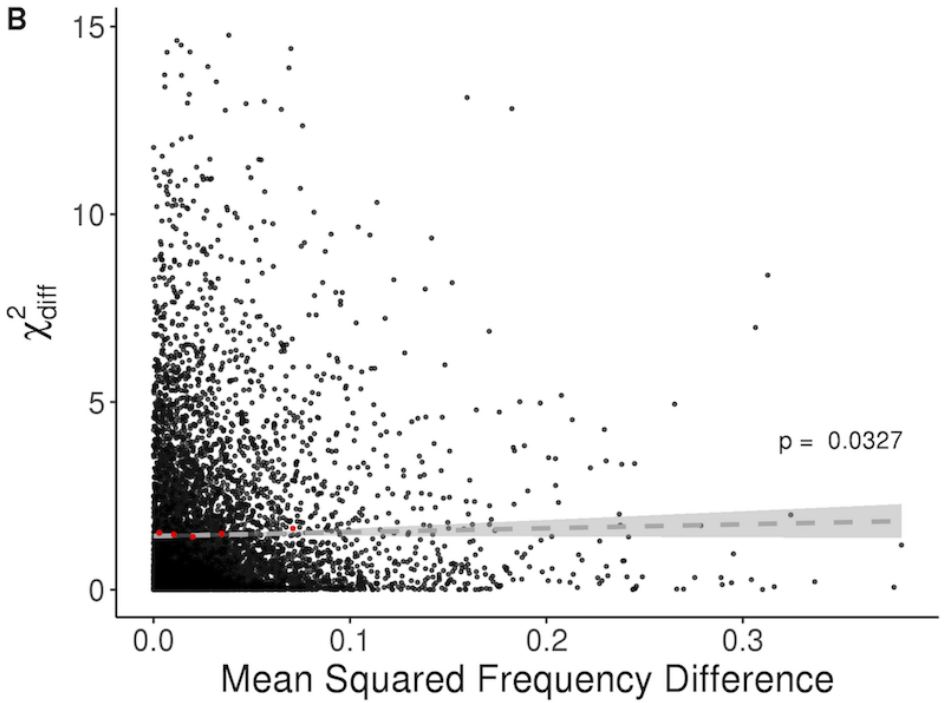


Recombination Rate

[Bitarello & Mathieson (2020), *G3*]

Observation: LOA is somewhat dependent on recombination rate

Prediction: Differences in effect sizes depend on allele frequency differences



[Bitarello & Mathieson (2020), *G3*]

$$N_{AFR} \sim 8,800$$

$$N_{EUR} \sim 350,000$$

$$\chi^2_{diff} = \left[\frac{\beta_{eur} - \beta_{afr}}{\sqrt{SE^2_{eur} + SE^2_{afr}}} \right]^2$$

Observation: Difference in effect sizes increase with allele frequency differences across ancestries

Assuming there are differences in marginal effect sizes

Assuming there are differences in marginal effect sizes

$$PRS_1^C = \alpha PRS_{AFR} + (1-\alpha)PRS_{EUR}$$

Marquez-Luna *et al.* (2018) *Genet Epidem*

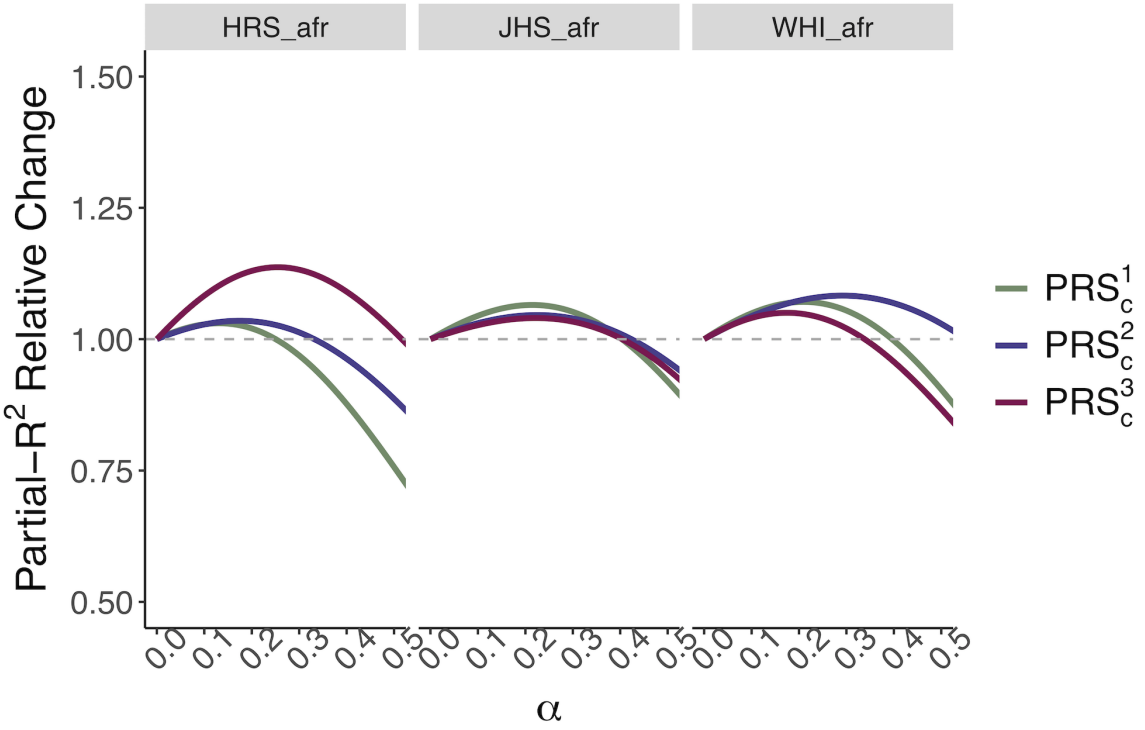
$$PRS_2^C = \alpha(1-p_{eur,j})PRS_{afr,j} + (1-\alpha+\alpha p_{eur,j})PRS_{EUR}$$

Bitarello & Mathieson (2020), *G3*

$$PRS_3^C = \alpha\left[\sum_{i\in AFR}\beta_{i,afr}G_i\right] + (1-\alpha)\left[\sum_{i\in AFR}\beta_{i,eur}G_i\right] + \left[\sum_{i\in EUR}\beta_{i,eur}G_i\right]$$

Bitarello & Mathieson (2020), *G3*

Prediction: Including ancestry-specific effect sizes improves accuracy for admixed individuals



[Bitarello & Mathieson (2020), *G3*]

Take Home Messages

- LD and SFS contribute to LOA across ancestries
- not enough to explain entire LOA
- marginal effect sizes differences occur
- better testing with larger NEA sample sizes

Future work

- optimizing ancestry-sensitive approach
- explore ancestry-dependent gene-gene interactions
- include more co-variates?

Acknowledgements

Iain Mathieson

Neale Lab

UK Biobank

Women's Health Initiative

Jackson Heart Study

Health and Retirement Study

Charles E. Kaufman Foundation

A SUPPORTING ORGANIZATION OF THE PITTSBURGH FOUNDATION

Perelman School of Medicine
University of Pennsylvania

THE PITTSBURGH FOUNDATION

NIH
NIGMS

Thank you!

Questions?