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Polygenic Score Workshop

Part 2: Evaluating Polygenic Scores

Jodi Thomas

24th July 2025

Adelaide Medical School

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Using Statistics to Evaluate PGS

- Data
- Statistics to evaluate PGS
  - Regression
  - R^2
  - Nagelkerke's R^2
  - R^2 on the liability scale
  - Odds Ratio by decile of PGS
  - AUC
- Applications
- Limitations
- Example

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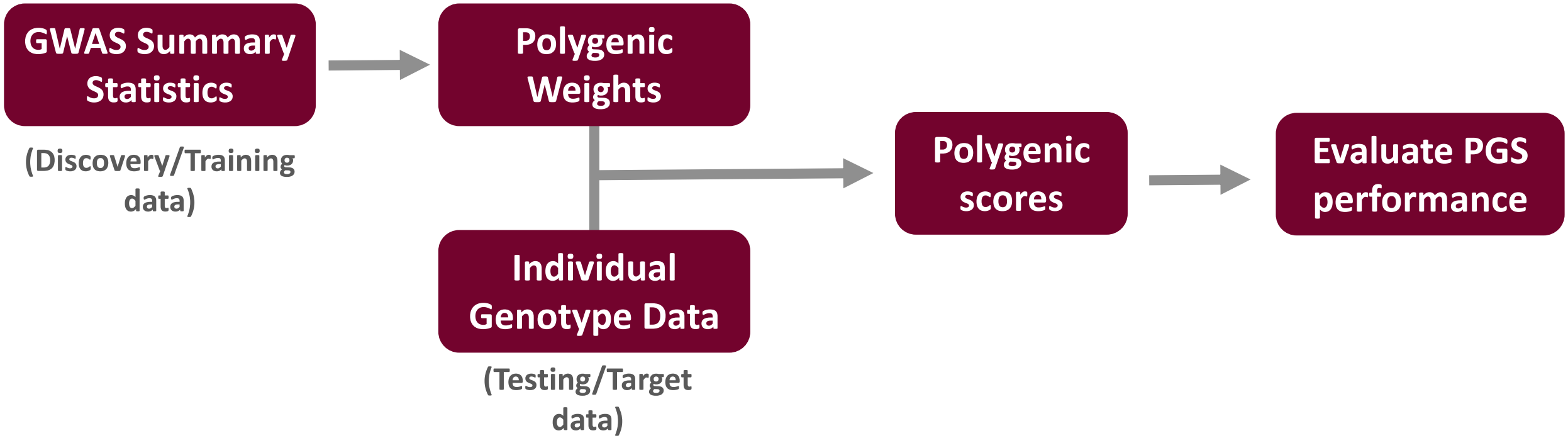
Data



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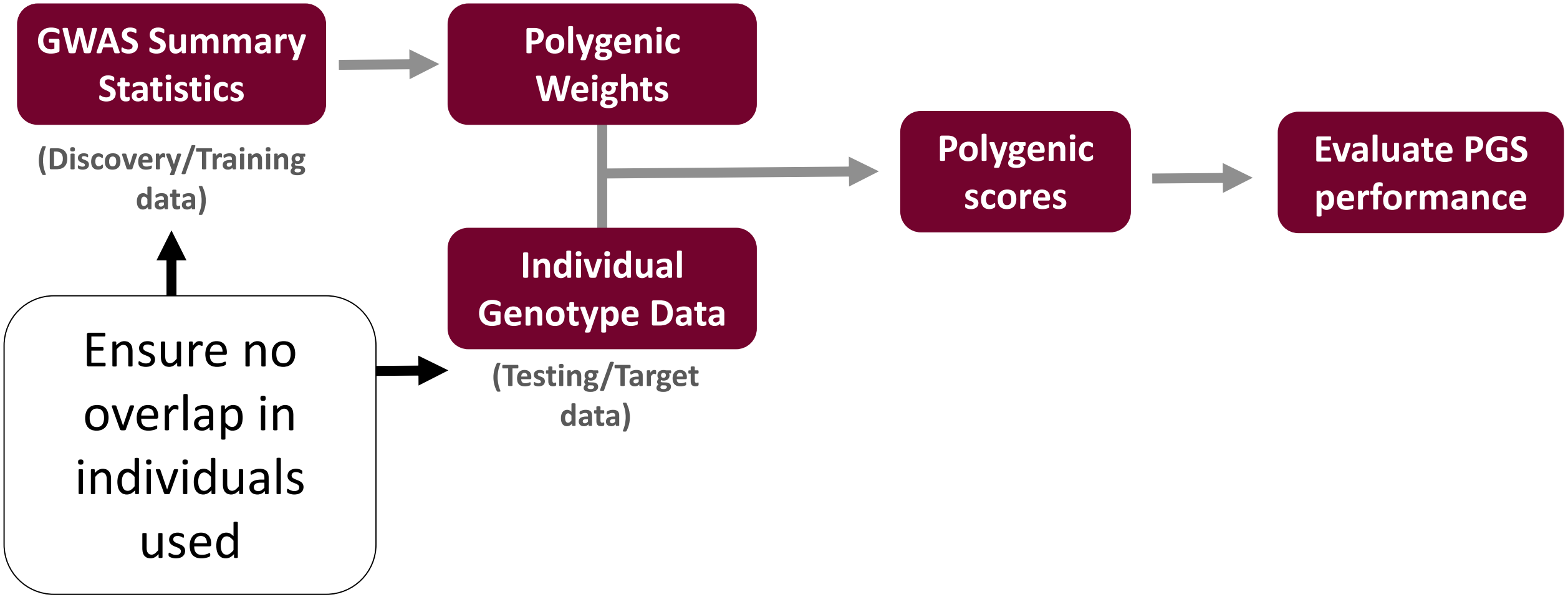
Data



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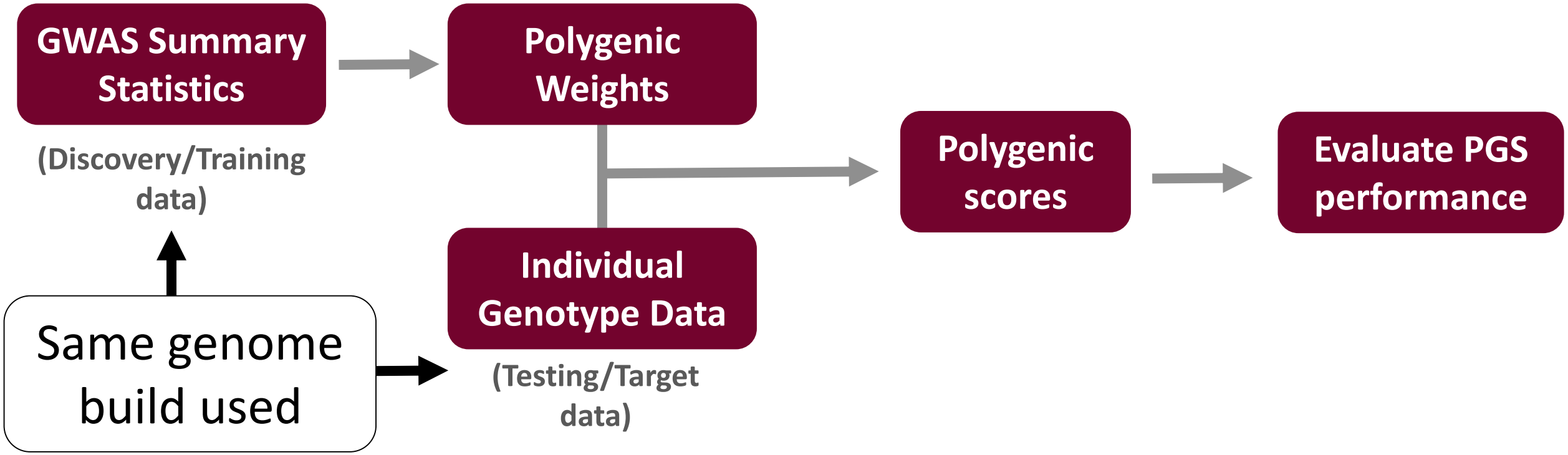
Data



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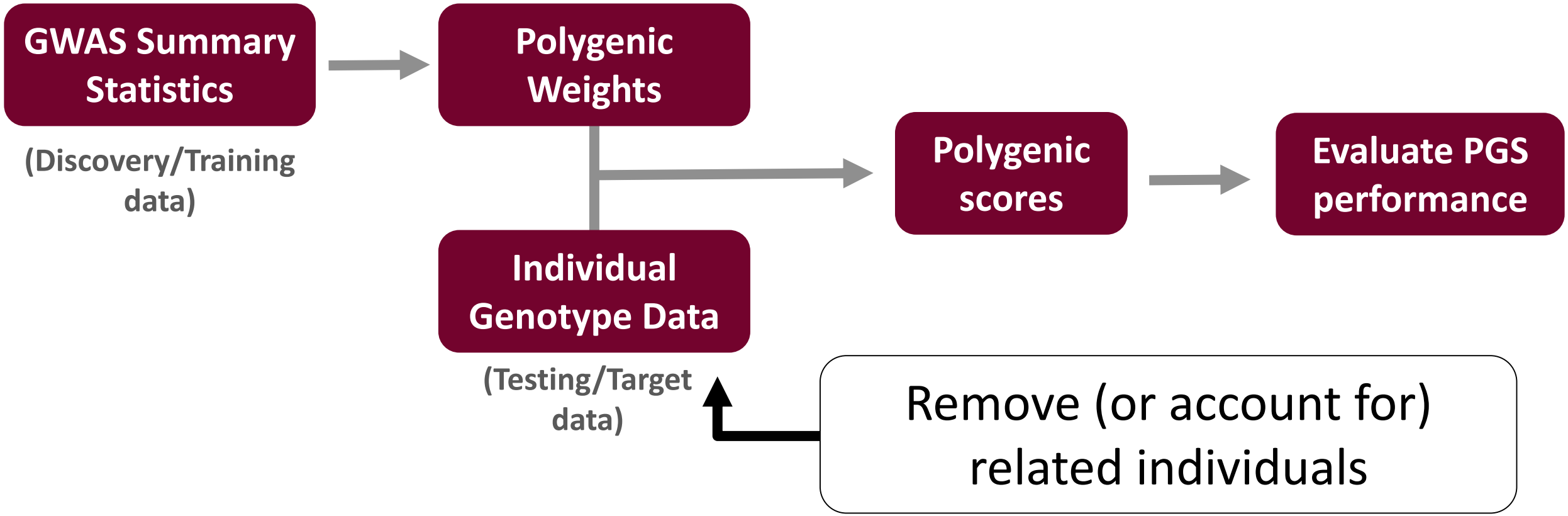
Data



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Data

FID	IID	PGS	Sex	PC1	PC2	PC3	PC4	PC5	PC6	Epilepsy
HG00096	HG00096	-0.03122	1	0.000643	0.066432	-1.47E-02	-0.036	-0.01636	-0.02094	0
HG00097	HG00097	0.007768	2	0.001414	0.073602	8.82E-03	-0.02058	-0.01168	0.022409	0
HG00099	HG00099	-0.04946	2	0.002647	0.07177	-2.10E-02	-0.00609	-0.01414	-0.00713	0
HG00101	HG00101	-0.01496	1	0.001698	0.085445	-1.57E-02	-0.00289	-0.03352	-0.01412	1
HG00102	HG00102	-0.04752	2	0.004411	0.069636	1.76E-06	-0.02643	-0.04776	-0.03145	0
HG00103	HG00103	-0.02364	1	-0.00431	0.057179	-8.19E-03	-0.01349	0.015997	-0.01207	0

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Binary Traits

Continuous Traits

Regression

- Regression model: Trait ~ PGS + covariates

- Linear regression for continuous trait (e.g. height)
- Logistic regression for binary trait (e.g. case/control)

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Binary Traits

Continuous Traits

Regression

- Regression model: Trait ~ PGS + covariates

- Linear regression for continuous trait (e.g. height)
- Logistic regression for binary trait (e.g. case/control)

- Is there a significant association between trait and PGS?
- Is the association in the expected direction?

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Continuous Traits

R^2 (Variance Explained)

- From the **linear regression**, estimate the R^2 that is attributable to the PGS
- R^2(full model) – R^2(covariates only model)
- Proportion of variance in the outcome variable explained by the PGS

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Continuous Traits

R^2 (Variance Explained)

- Advantage
  - Comparable to SNP-based heritability (h^2)

- Limitation
  - R^2 can't be compared across outcome traits on different scales (make sure to standardise outcome traits to allow comparison)

Nagelkerke's R^2

- From the **logistic regression**, estimate Nagelkerke's R^2 that is attributable to the PGS

- Nagelkerke's R^2(full model) – Nagelkerke's R^2(covariates only model)

- A pseudo-R^2 value from 0 - 1
- A relative measure of model fit representing an approximation of explained variance

Nagelkerke's R^2

- Advantage
  - A familiar metric that is easy to compute
- Limitations
  - A relative measure of fit and can't be interpreted as 'proportion of variance explained' like linear R^2
  - On the binary observed scale
    - This depends on the case/control ratio in your sample
    - Can't be compared across studies with different case/control ascertainment
  - Is not comparable to SNP-based heritability (h^2)

Observed R^2

- Explains variation in case/control status
- Depends on case/control ratio in sample

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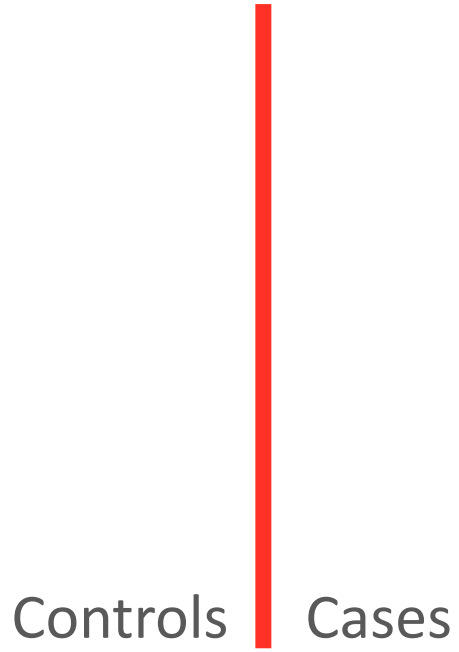
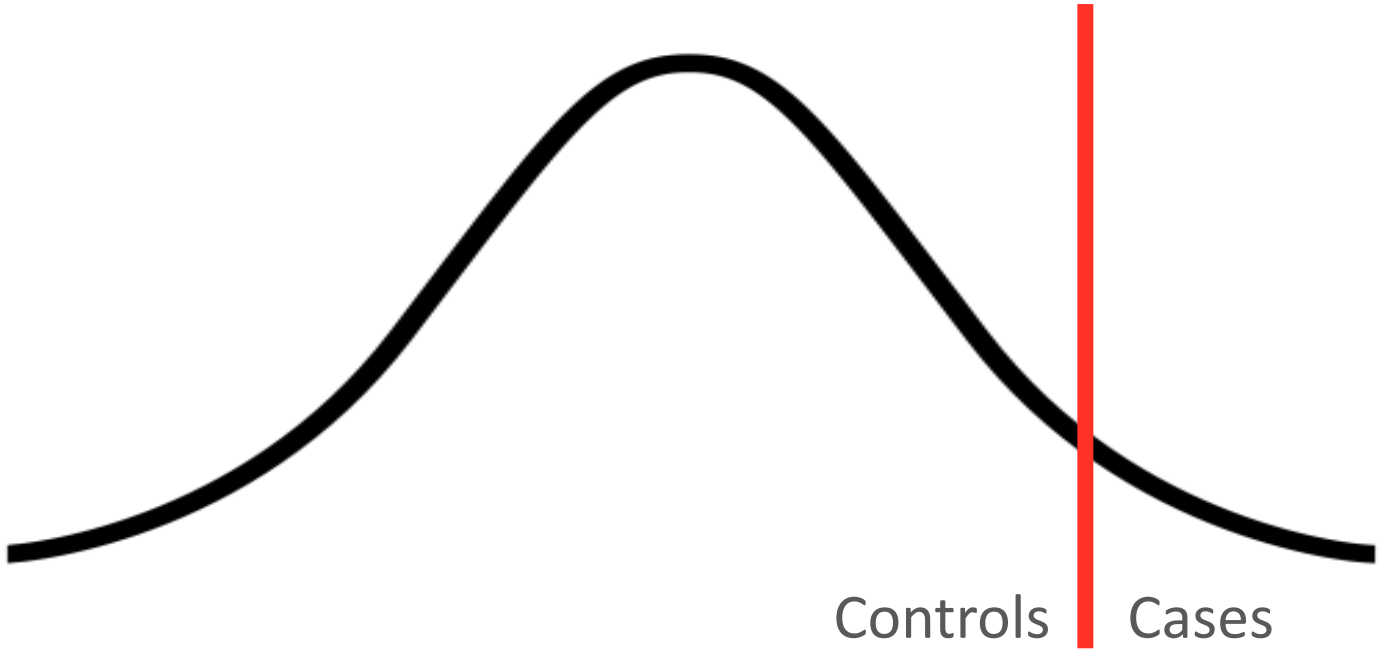
- Explains variation in case/control status
- Depends on case/control ratio in sample

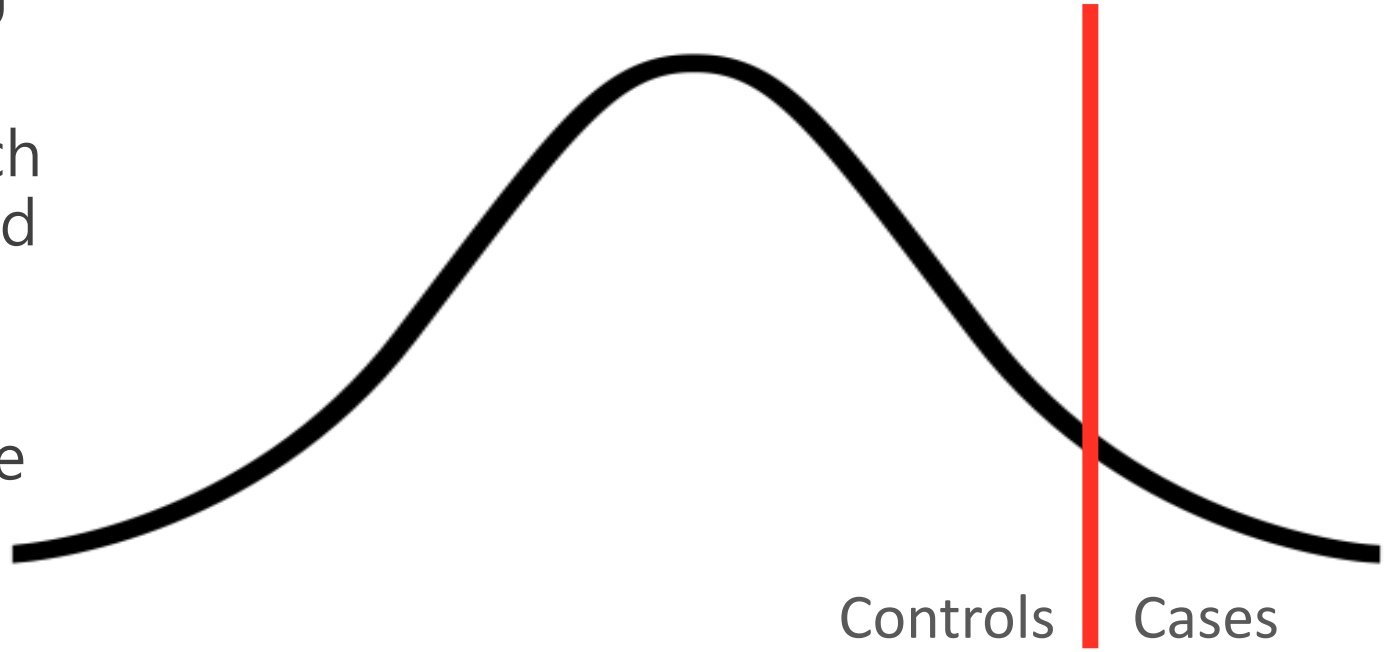


Liability R^2



Liability R^2

- Assumes there's an underlying continuous risk for disease
- Liability R^2 estimates how much of that continuous, unobserved risk is explained by the PGS
- Adjusts for both population disease prevalence and sample ascertainment



Lee SH, et al., *A Better Coefficient of Determination for Genetic Profile Analysis.* Genetic Epidemiology, 2012. 36(3):214-224.

Observed R^2 from linear regression

Calculate constants:

- **K = population prevalence**
- **P = sample prevalence**
- **t = the threshold on the normal distribution which truncates the proportion of disease prevalence**
- **z = density at t**
- **m = mean liability = z/K**

Compute C and θ using formulas:

- $C = \frac{K(1-K)}{z^2}\frac{K(1-K)}{P(1-P)}$
- $\theta = m\frac{P-K}{1-K}\left(m\frac{P-K}{1-K} - t\right)$

Calculate liability R^2:

$$R^2_{liability} = \frac{R^2_{observed}C}{1+R^2_{observed}\theta C}$$

Liability R^2

- Steps
  - Run linear regression (even though outcome is binary)
  - Adjust R^2 to the liability scale
  - R^2 liability (full model) – R^2 liability (covariates only model)

- Proportion of variance in the unobserved liability (risk) for a binary trait that is explained by the PGS

R^2 on the Liability Scale

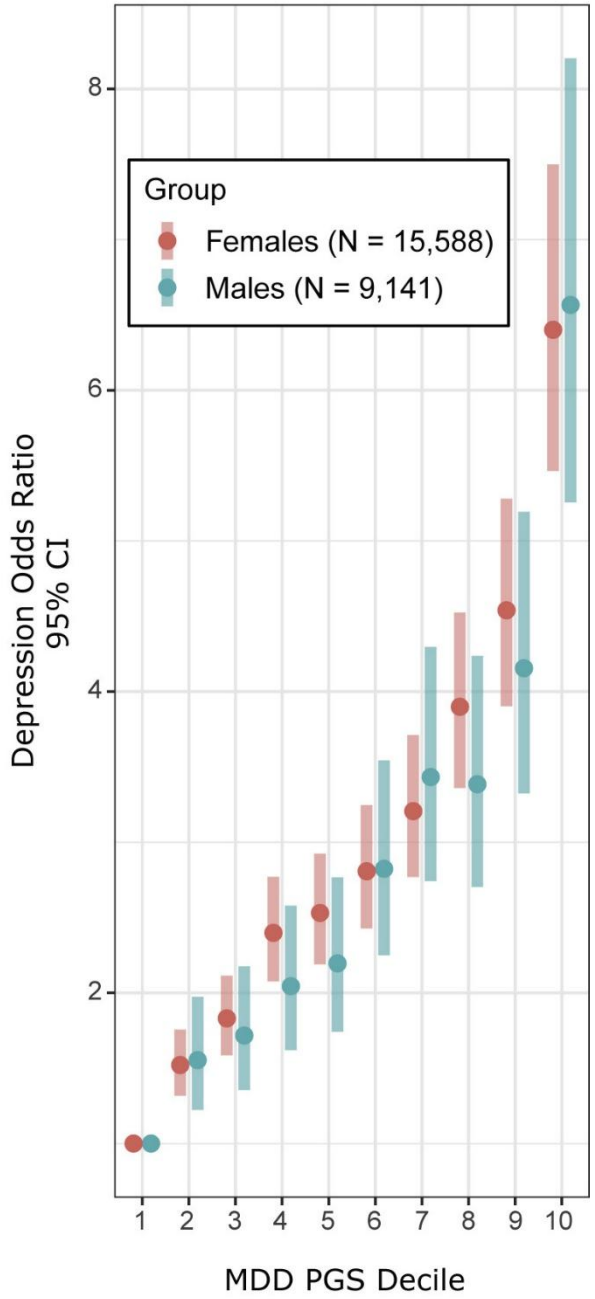
- Advantages
  - Can compare across studies
  - Comparable to SNP-based heritability (h^2)

- Limitations
  - Requires the population prevalence of the trait
  - Assumes an underlying liability threshold model

Odds Ratio by Decile of PGS

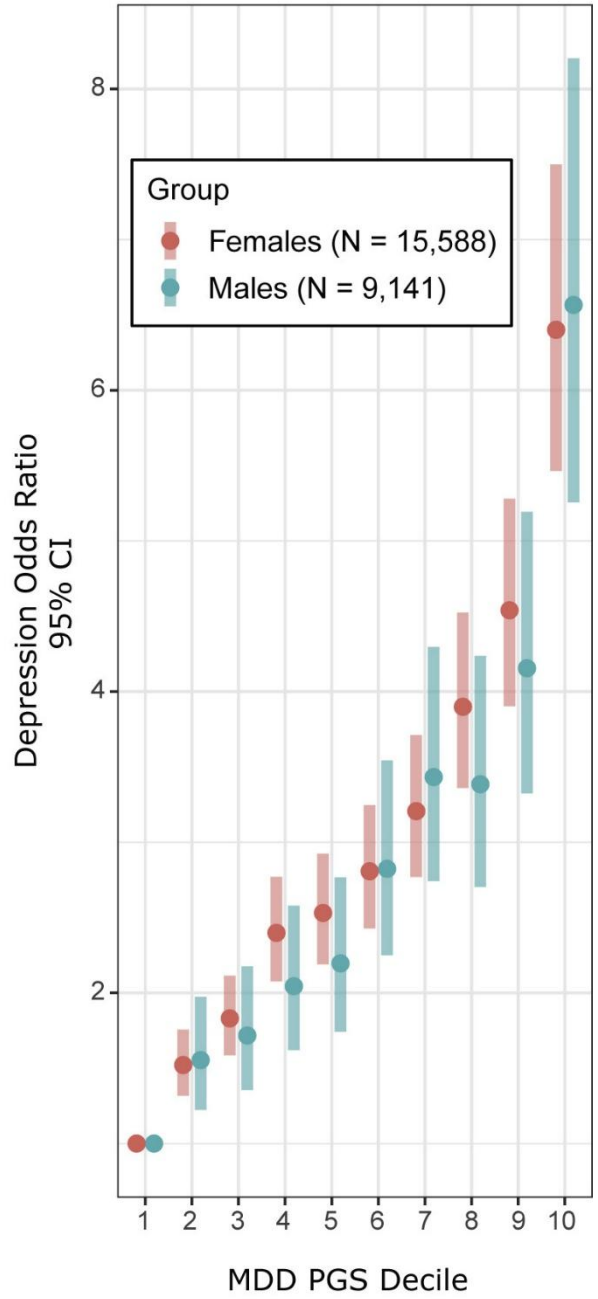
- Cut PGS distribution into deciles
- Run logistic regression: Trait(case/control) ~ PGS(deciles) + covariates
- Odds ratio of each PGS decile compared to the:
  - First (lowest) PGS decile
  - Middle PGS decile (more recently)

Binary Traits



Mitchell BL, et al., *The Australian Genetics of Depression Study: New risk loci and dissecting heterogeneity between subtypes. Biol Psychiatry, 2022. 92(3):227-235.*

Binary Traits



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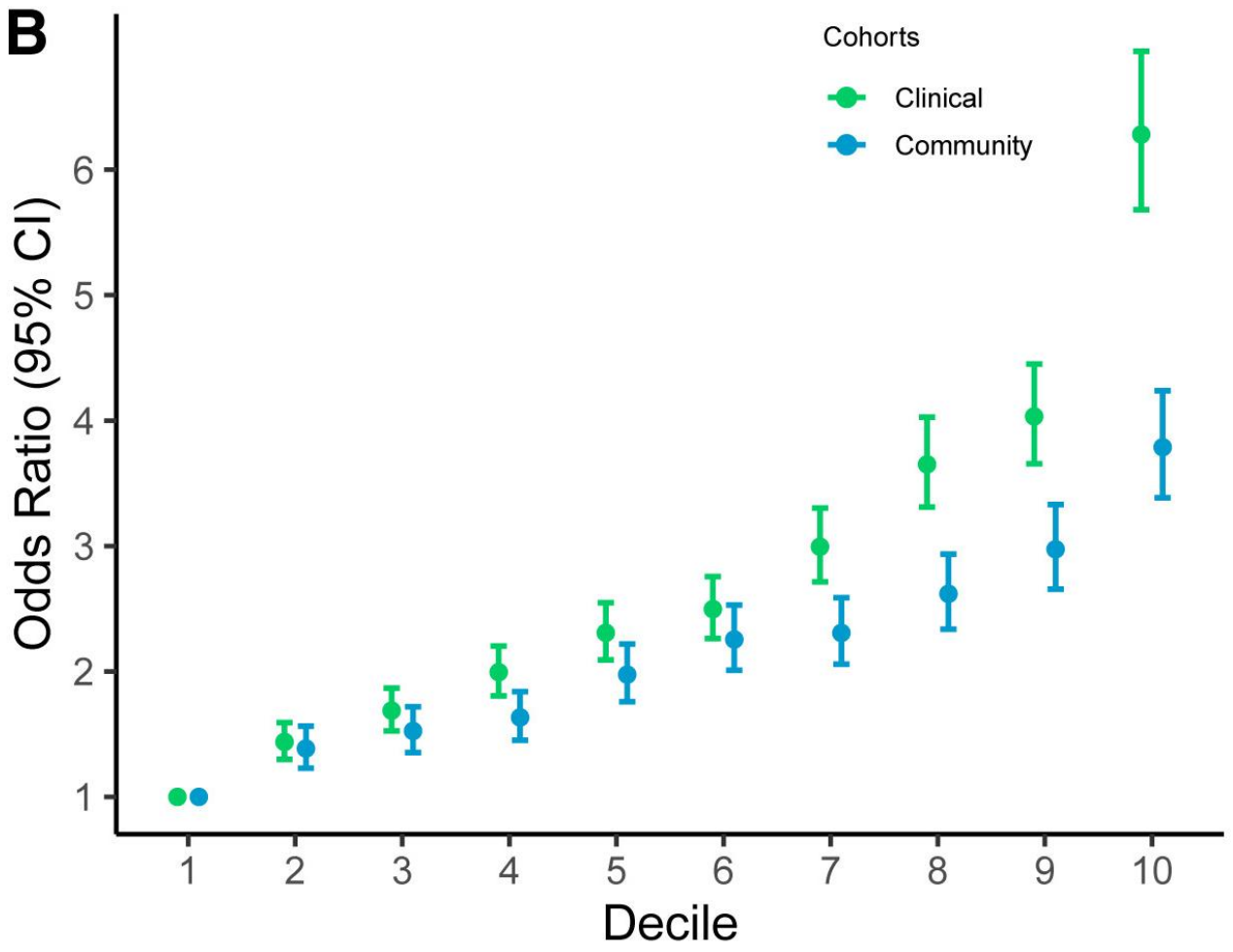
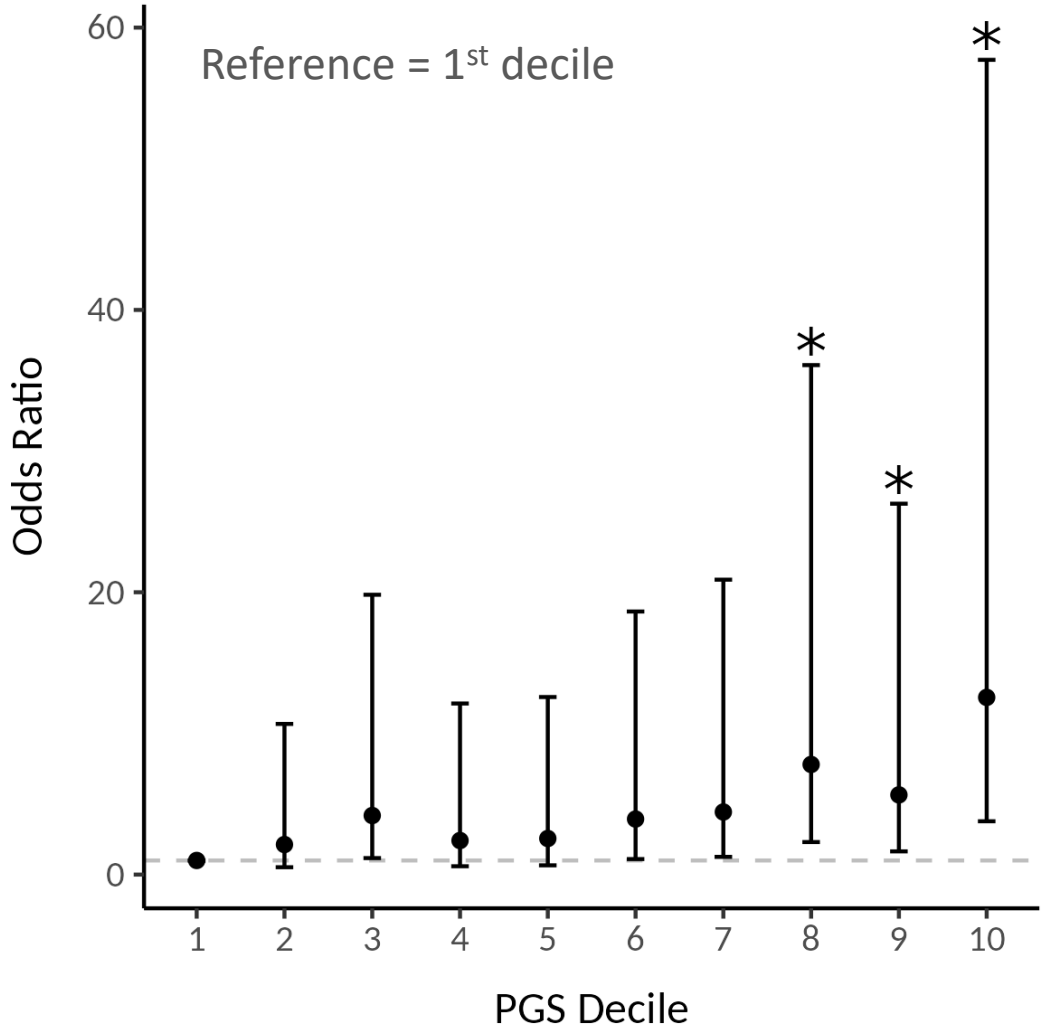
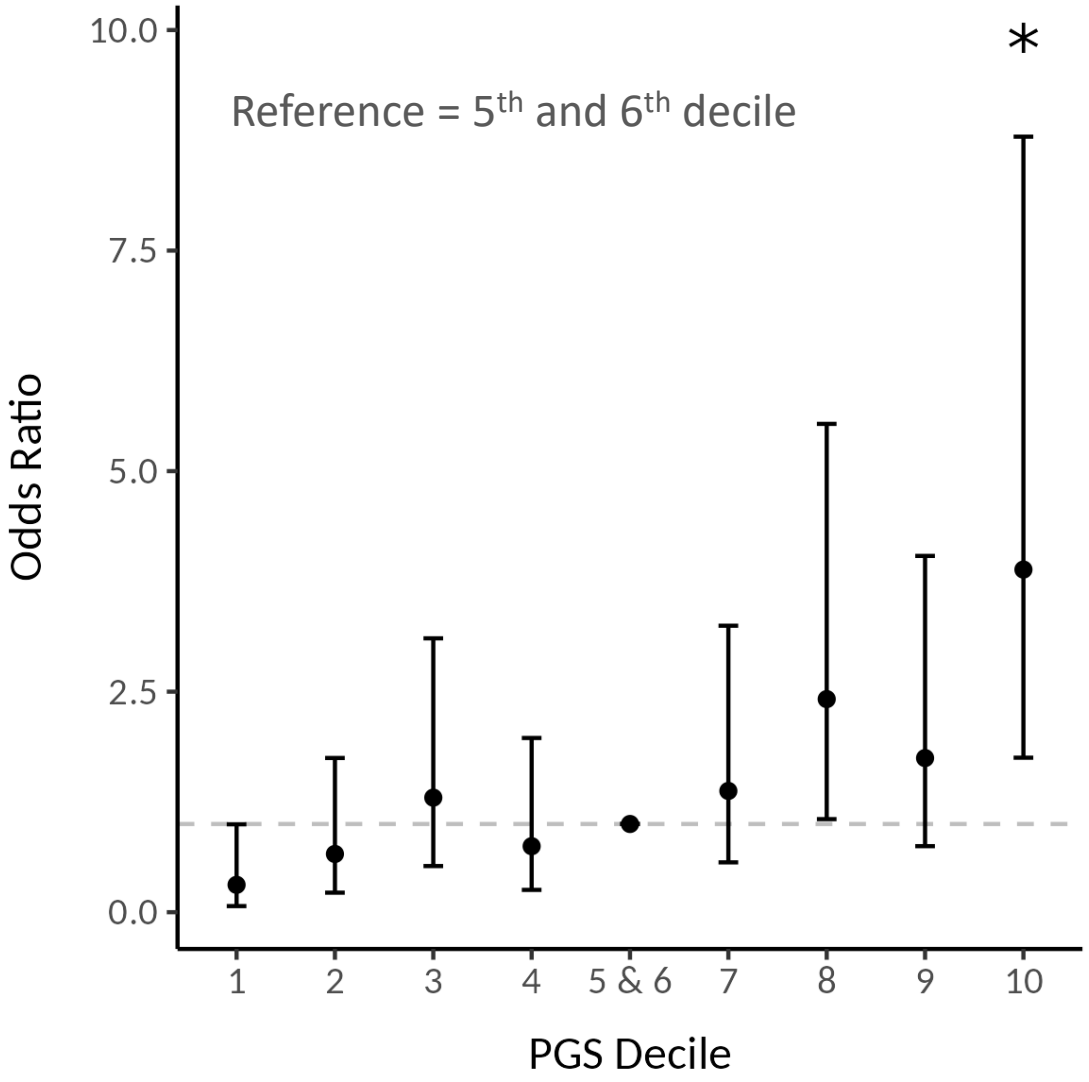


Adams MJ, et al., *Trans-ancestry genome-wide study of depression identifies 697 associations implicating cell types and pharmacotherapies. Cell, 2025. 188:1-13.*

Example from workshop (simulated data)

Binary Traits





Odds Ratio by Decile of PGS

- Advantage
  - Practical and interpretable way to visualise risk stratification

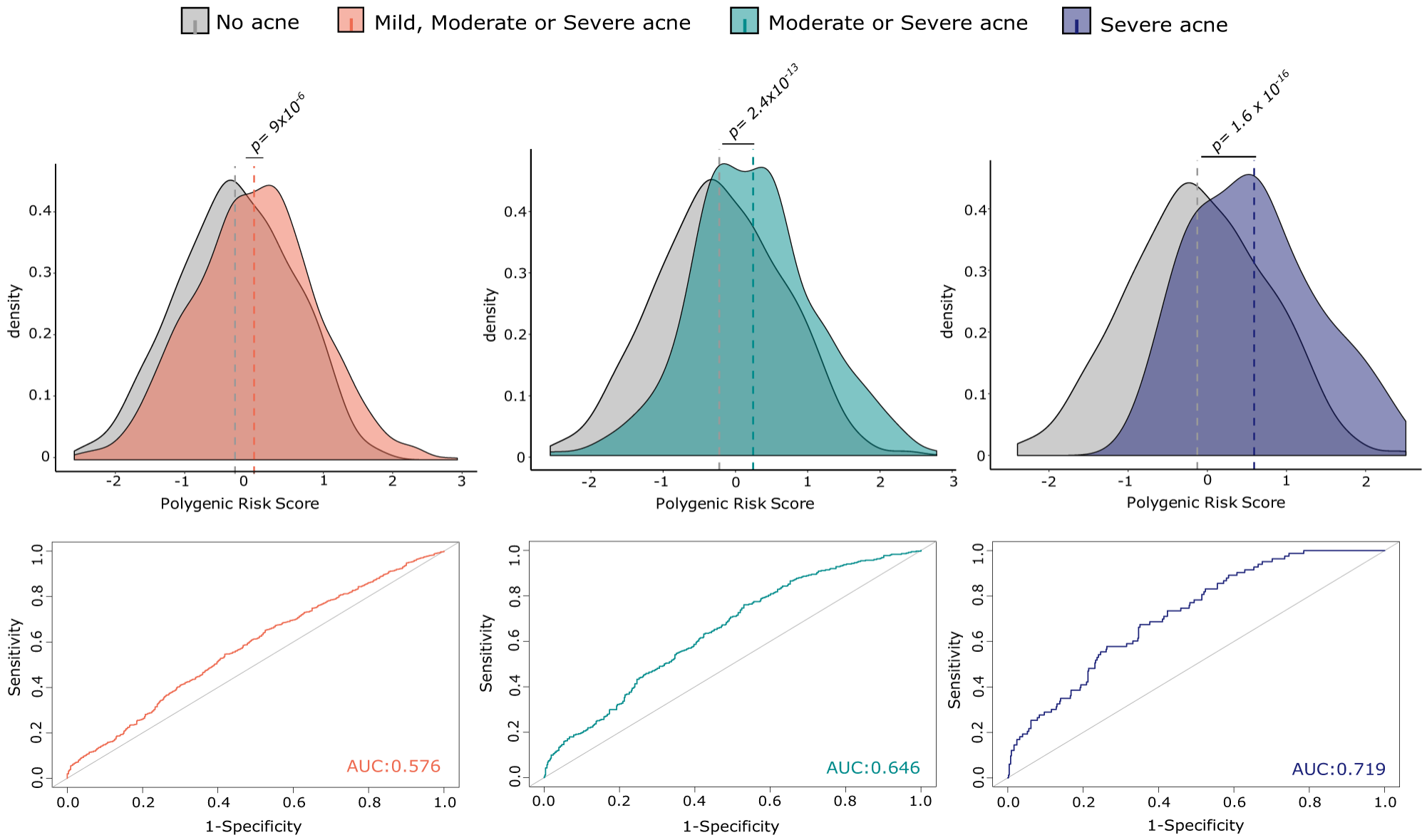
- Limitations
  - Doesn't take into account proportion of cases and controls in your data
    - Will look much more impressive if you have a data set with 50% cases and 50% controls, compared to a population sample.
  - Categorising PGS into deciles loses information

AUC

- Area Under the Receiver Operating Characteristic Curve

- Probability that a randomly selected case has a higher test score than a randomly selected control
  - 0.5 = no discrimination of cases and controls
  - 1 = perfect discrimination

Binary Traits



Mitchell BL, et al., *Genome-wide association meta-analysis identifies 29 new acne susceptibility loci. Nat Commun, 2022. 13(1):702.*

AUC

- Advantages
  - Well established measure
  - Independent to proportion of cases and controls in sample
- Limitations
  - Problem with genetic interpretation
    - PGS is a proxy (AUC is limited by how well the PGS captures genotype–phenotype associations)
    - The maximum AUC achievable depends on the heritability of the disease
    - A low AUC doesn’t necessarily mean genetics don’t matter

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Best to report multiple measures

Make your results accessible to both geneticists and clinicians

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Applications

Discovery Sample	Target Sample	Application	Biological Insight
Disorder A	Disorder A	Show polygenicity	PGS can predict outcomes even without genome-wide hits
Disorder A	Disorder B	Test pleiotropy	Reveals shared genetic architecture between conditions
Disorder A	Subtypes of Disorder A	Investigate heterogeneity	Subtypes may have distinct genetic contributions
Disorder A	Disorder A + environment data	Explore GxE	Genes may act differently depending on environmental context
Disorder A	Environmental exposure or presence of a trait	Explore gene-environment/trait correlations	Certain exposures/traits may be genetically linked
Disorder A	General population / clinical cohorts	Identify at-risk individuals	Risk stratification to identify individuals at high genetic risk

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Limitations

- Individual-level prediction is not accurate enough for most phenotypes
  - Not reliable for individual diagnosis or decision-making
- Difficult to interpret what the PGS is truly capturing
  - Includes many variants with unknown function
  - Predictive power may reflect not only the causal effect of genetic variants but also gene-environment correlations, population stratification, indirect genetic effects, assortative mating
- Poor transferability across ancestries
  - PGS mainly developed in European populations and underperform when used in other ancestries

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Example

Do polygenic scores (PGS) for Cerebral Palsy and comorbid traits associate with Cerebral Palsy?

These slides from the workshop have been removed due to being unpublished results

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Github Repository
Polygenic Score Workshop

https://github.com/jodithea/Polygenic_score_workshop